

# THE QUARTERLY JOURNAL OF MEDICINE

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# CONTENTS

## NUMBER 69, OCTOBER 1924

	PAGE
The Effect of Iodine on Hyperthyroidism in Man. By S. J. Cowell and E. Mellanby . . . . .	1
A Clinical Study of van den Bergh's Test in Jaundice. By C. H. Andrewes . . . . .	19
The Relation between the Basal Metabolic Rate and the Pulse-pressure in Conditions of Disturbed Thyroid Function. By H. Whitridge Davies and John Eason . . . . .	36
Some Factors concerned in the Aetiology of Tetany in Children. By Grace H. Anderson and Stanley Graham . . . . .	62
On the Pathology of Nephritis associated with Oedema, as illustrated by Six Cases. By S. C. Dyke. With Plates 1-3 . . . . .	77
Spontaneous Subarachnoid Haemorrhage. By C. P. Symonds. With Plate 4 . . . . .	93
Cholesterol in the Blood in Cases of Gall-stones. By J. M. H. Campbell . . . . .	123

## NUMBER 70, JANUARY 1925

Some Factors of Significance in Adolescent Goitre. By H. Gardiner-Hill, P. C. Brett, and J. Forest Smith . . . . .	133
A Case of Virilism associated with a Suprarenal Tumour: Recovery after its Removal. By Gordon Holmes. With Plate 5 . . . . .	143
Epidemic Encephalitis: the Second Winnipeg Outbreak. By William Boyd. With Plates 6 and 7 . . . . .	153
The Sugar Content of the Blood in Normal and Under-nourished Children, and the Effect of Fat on the Absorption of Carbohydrate. By Muriel J. Brown . . . . .	175
The Geographical Distribution of Exophthalmic Goitre in the British Isles. By J. M. H. Campbell . . . . .	191
Progressive Lipodystrophy. By W. N. Boog Watson and W. T. Ritchie. With Plates 8 and 9 . . . . .	224

## NUMBER 71, APRIL 1925

The Blood-urea and its Estimation in Diabetes Mellitus. By Charles E. Brunton . . . . .	241
Lymphoblastic Erythrodermia. By James H. Sequeira and Philip N. Panton. With Plates 10 and 11 . . . . .	250
Changes in the Blood in Anaesthesia. By Dorothy G. E. Potter . . . . .	261
The Tolerance of the Body for Urea in Health and Disease. By H. E. Archer and G. D. Robb . . . . .	274
Calcium and Magnesium in some Pathological Sera. By Elsie Watchorn . . . . .	288
The Relation of Infection to Diabetic Coma. By George Graham . . . . .	294
The Spinal Fluid Sugar in Encephalitis. By James L. Halliday . . . . .	300
Pituitary Obesity in Adolescence. By H. Gardiner-Hill, I. Jones, and J. Forest Smith. With Plates 12 and 13 . . . . .	309
Carbohydrate Tolerance in Myxoedema. By H. Gardiner-Hill, P. C. Brett, and J. Forest Smith . . . . .	327

## NUMBER 72, JULY 1925

	PAGE
Four Cases of Congenital Dextrocardia, including a Case with Sino-auricular Block. By Leonard Abrahamson. With Plates 14-16 . . . . .	335
Acute Ileocolitis in Children. By Robert Cruickshank . . . . .	339
The Mode of Inheritance of Hereditary Ataxia. By W. Russell Brain . . . . .	351
Heredity in Polycystic Disease of the Kidneys. By H. W. B. Cairns. With Plate 17 . . . . .	359
Critical Review. Cholesterol in Health and Disease. By J. M. H. Campbell . . . . .	393
Proceedings of the Association of Physicians of Great Britain and Ireland	1924 <i>at end of volume</i>

## INDEX OF CONTRIBUTORS

	PAGE
ABRAHAMSON, L. Four Cases of Congenital Dextrocardia, including a Case with Sino-auricular Block. With Plates 14-16 . . . . .	335
ANDERSON, G. H. Some Factors concerned in the Aetiology of Tetany in Children . . . . .	62
ANDREWES, C. H. A Clinical Study of van den Bergh's Test in Jaundice . . . . .	19
ARCHER, H. E. The Tolerance of the Body for Urea in Health and Disease . . . . .	274
BOYD, W. Epidemic Encephalitis: the Second Winnipeg Outbreak. With Plates 6 and 7 . . . . .	153
BRAIN, W. R. The Mode of Inheritance of Hereditary Ataxia . . . . .	351
BRETT, P. C. Some Factors of Significance in Adolescent Goitre . . . . .	133
————— Carbohydrate Tolerance in Myxoedema . . . . .	327
BROWN, M. J. The Sugar Content of the Blood in Normal and Under-nourished Children, and the Effect of Fat on the Absorption of Carbohydrate . . . . .	175
BRUNTON, C. E. The Blood-urea and its Estimation in Diabetes Mellitus . . . . .	241
CAIRNS, H. W. B. Heredity in Polycystic Disease of the Kidneys. With Plate 17 . . . . .	359
CAMPBELL, J. M. H. Cholesterol in the Blood in Cases of Gall-stones . . . . .	123
————— The Geographical Distribution of Exophthalmic Goitre in the British Isles . . . . .	191
————— Critical Review. Cholesterol in Health and Disease . . . . .	393
COWELL, S. J. The Effect of Iodine on Hyperthyroidism in Man . . . . .	1
CRUICKSHANK, R. Acute Ileocolitis in Children . . . . .	339
DAVIES, H. W. The Relation between the Basal Metabolic Rate and the Pulse-pressure in Conditions of Disturbed Thyroid Function . . . . .	36
DYKE, S. C. On the Pathology of Nephritis associated with Oedema, as illustrated by Six Cases. With Plates 1-3 . . . . .	77
EASON, J. The Relation between the Basal Metabolic Rate and the Pulse-pressure in Conditions of Disturbed Thyroid Function . . . . .	36
GARDINER-HILL, H. Some Factors of Significance in Adolescent Goitre . . . . .	133
————— Pituitary Obesity in Adolescence. With Plates 12 and 13 . . . . .	309
————— Carbohydrate Tolerance in Myxoedema . . . . .	327
GRAHAM, G. The Relation of Infection to Diabetic Coma . . . . .	294
GRAHAM, S. Some Factors concerned in the Aetiology of Tetany in Children . . . . .	62
HALLIDAY, J. L. The Spinal Fluid Sugar in Encephalitis . . . . .	300
HOLMES, G. A Case of Virilism associated with a Suprarenal Tumour: Recovery after its Removal. With Plate 5 . . . . .	143

	PAGE
JONES, I. Pituitary Obesity in Adolescence. With Plates 12 and 13 . . .	309
MELLANBY, E. The Effect of Iodine on Hyperthyroidism in Man . . .	1
PANTON, P. N. Lymphoblastic Erythrodermia. With Plates 10 and 11 . . .	250
POTTER, D. G. E. Changes in the Blood in Anaesthesia . . . . .	261
RITCHIE, W. T. Progressive Lipodystrophy. With Plates 8 and 9 . . .	224
ROBB, G. D. The Tolerance of the Body for Urea in Health and Disease . .	274
SEQUEIRA, J. H. Lymphoblastic Erythrodermia. With Plates 10 and 11 . .	250
SMITH, J. F. Some Factors of Significance in Adolescent Goitre . . .	138
——— Pituitary Obesity in Adolescence. With Plates 12 and 13 . . .	309
——— Carbohydrate Tolerance in Myxoedema . . . . .	327
SYMONDS, C. P. Spontaneous Subarachnoid Haemorrhage. With Plate 4 . .	93
WATCHORN, E. Calcium and Magnesium in some Pathological Sera . . .	288
WATSON, W. N. B. Progressive Lipodystrophy. With Plates 8 and 9 . . .	224





## THE EFFECT OF IODINE ON HYPERTHYROIDISM IN MAN

By S. J. COWELL AND E. MELLANBY

(From the Royal Infirmary, Sheffield, and the Department of Pharmacology  
in the University)

### *Introduction.*

WHILE it is generally recognized that there is an intimate relationship

### ERRATA

No. 68, page 422. Under *Remarks* the details of time following  
Cases III and IV should be deleted

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plastic glands changing to a cubical or flat shape and the alveoli becoming round and regular in contour and filled with an eosin-staining colloid. Other observations by Marine and his co-workers (2) on the goitres found in brook trout in certain breeding-ponds in America, and the reversion of their hyperplastic thyroids to normal structure and size following the introduction into the water of sea-water fish (containing iodine) as food, or iodides themselves, were of a parallel nature.

It is of interest to note that true hyperplasia of the thyroid, whether associated with symptoms of hyperthyroidism or not, is always related to a diminished iodine content, and the degree of hyperplasia is generally greater as the iodine in the gland diminishes. In fact absence of iodine seems to be a controlling factor in the development of this type of change, but whether it can be inferred that there has never been an adequate supply of iodine or that conditions have arisen which have driven the store of iodine out of the gland and out of the body is not known.

In addition to the evidence of the relation between iodine and thyroid hyperplasia there is also evidence of the relation between iodine and the development of colloid goitre. As the result of the endeavours of different workers, particularly Marine (3) in America, to eliminate goitres from districts

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### *Introduction.*

WHILE it is generally recognized that there is an intimate relationship between the supply of iodine to the body and the histological structure of the thyroid gland, it is not so evident that, either as the direct outcome of this connexion, or possibly, to some extent at least, independently of this relationship, iodine may have a potent influence on the regulation of metabolic processes in the body. Of the close connexion between the thyroid gland and iodine, both from a chemical and structural point of view, there is overwhelming evidence. The hyperplasia of the thyroid glands of dogs and other animals could be cured by Marine (1) in the course of a few weeks by iodine. The glands reverted to the normal structure, the columnar cells surrounding the alveoli in the hyperplastic glands changing to a cubical or flat shape and the alveoli becoming round and regular in contour and filled with an eosin-staining colloid. Other observations by Marine and his co-workers (2) on the goitres found in brook trout in certain breeding-ponds in America, and the reversion of their hyperplastic thyroids to normal structure and size following the introduction into the water of sea-water fish (containing iodine) as food, or iodides themselves, were of a parallel nature.

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where they are prevalent, it has been found that small doses of iodides given to children prevent the development of these changes in the thyroid, and that, after prolonged treatment, they may bring about in some cases a reversion to the normal size of thyroids already enlarged.

But while iodine influences the structure both of hyperplastic thyroids in animals and of colloid thyroids in men, it is not obvious that it also influences the metabolism. The glands in these cases, although abnormal in structure, are generally not associated with any obvious abnormality of bodily function, nor does their reversion to normal following the administration of iodine bring about, so far as is known, any great change in the metabolic processes.

When we try to extend these facts to the problem of hyperthyroidism, we find great difficulties both of a theoretical and practical nature. Two questions present themselves for consideration: (1) Is hyperplasia of the thyroid gland always associated with some degree of hyperthyroidism? and (2) Is the thyroid gland always hyperplastic in human hyperthyroidism, and if so, is this type of hyperplasia similar in all respects to that found in animals? As regards the first question it can be said that in animals there may certainly be great hyperplasia without any obvious symptoms of hyperthyroidism. Slight degrees of hyperplasia may sometimes be found in human thyroids taken from subjects in whom no signs of hyperthyroidism had been detected, and goitres removed from patients without toxic symptoms may show the histological characters of active hyperplasia. It would appear, however, that in man any large degree of hyperplasia is not common in the absence of symptoms of hyperthyroidism, and Plummer (4) has said that 'if hyperplasia of the thyroid is of sufficient degree or extends over a long enough period, exophthalmos is almost sure to develop'.

It is also difficult to give a definite answer to the second question, viz. Is hyperthyroidism always associated with thyroid hyperplasia? In most cases it is certainly associated with thyroid abnormality, and this abnormality is most commonly hyperplasia or includes hyperplasia. However, Marine (5) found in 137 cases of exophthalmic goitre, where the gland was examined at autopsy or after operation, there was some degree of active hyperplasia in 60 per cent. of the cases only and the symptom-complex was not associated with either constant or characteristic changes in the thyroid. All he admits is that the proportion of glands with active hyperplasia at the time of operation is higher in a series of exophthalmic goitre cases than in cases of simple goitre. This statement, which has as its corollary the view that hyperplasia of the thyroid is secondary in character and is not the primary cause of hyperthyroidism, has been endorsed by MacCallum (6) and rests on evidence confirmatory of the observations made originally by Virchow (7). Naturally the view has been opposed by others, more especially by surgeons, including C. H. Mayo (8), because of the obvious effect on the symptoms that follow operative interference with the thyroid in exophthalmic goitre.

While, therefore, it is difficult to give definite answers to the above questions, the experience of those who, like Marine, have had exceptionally great

opportunities for studying the problem, indicates that although thyroid hyperplasia plays some part and probably an important part in hyperthyroidism, it is not the sole and possibly not even the primary cause of the symptoms.

During the past few years we have been making observations in Sheffield on conditions which tend to the production of thyroid hyperplasia in dogs, in the hope of showing what factors might possibly determine the thyroid changes commonly found in exophthalmic goitre in man. In a preliminary communication some of these have been mentioned by E. and M. Mellanby. This work, though by no means complete, indicates in a general way that those dietetic and environmental conditions which bring about the most rapid bodily growth, absolutely or relatively to the size of the diet, favour the development of hyperplasia, while any condition which prevents increase in body-weight tends to the production of small glands more normal in structure. In all cases iodine in the diet keeps the glands small. Probably for this reason there is a great difference between the effect of cod-liver oil and butter. Cod-liver oil contains a small amount of iodine, and when present in the diet the thyroids remain small and normal. Butter, on the other hand, has a definite tendency to produce hyperplasia. More detailed publication of these facts will follow later, but we wish to state here that on the basis of this experimental work all the patients treated for hyperthyroidism have been given a diet which, while qualitatively sound, is of small energy value. Consideration of the action of the diet itself in hyperthyroidism we will hold over to a later occasion, but we may say here that there is evidence that it plays a part in the production of results described in this paper.

As regards the action of iodine in the diet the evidence of earlier workers discussed above shows that a supply of this substance both prevents the development of thyroid hyperplasia and converts a hyperplastic into a normal gland. It might, therefore, be expected that in cases of hyperthyroidism associated with thyroid hyperplasia the effect of iodine would be to cause the gland to become normal. Marine and Lenhart (9) say that this does happen and that in 15 cases of undoubted exophthalmic goitre iodine was rapidly stored by the gland and produced involution to the colloid state, and that, in fact, the thyroid hyperplasia of exophthalmic goitre behaved towards iodine exactly as did simple thyroid hyperplasia in animals. Now if this be true it seems to clinch the question as to whether or not thyroid hyperplasia is responsible for hyperthyroidism, for after a few weeks of iodine medication the hyperplasia should disappear and the symptoms of hyperthyroidism should clear up if they are related as cause and effect. This certainly does not happen. Either, then, iodine does not produce the same effect on the thyroid apparatus in cases of hyperthyroidism as in simple hyperplasia or the hyperplasia is not the primary part of the mechanism responsible for the symptoms of hyperthyroidism. Although we have not been able to formulate definite views on this and many other problems in this investigation, we may say that our inclination is to the belief that iodine does not have the same effect on thyroid hyperplasia associated with hyperthyroidism as it does on simple hyperplasia of the thyroid. We agree that there is a strong

tendency for the gland to revert to the normal under the influence of iodine, but there seems to be another active factor tending to withdraw iodine or iodine-containing compounds away from the gland and so preventing this reversion.

While it is generally agreed that iodine does influence exophthalmic goitre, there is no unanimity as to what the action is or what is its value in treatment. Kocher (10) taught that the administration of potassium iodide must never be carried out in exophthalmic goitre, and, on the whole, this advice has been taken. As evidence of this fact may be mentioned the discussion on the treatment of exophthalmic goitre at the Royal Society of Medicine in 1923. No speaker mentioned iodine or any preparation of iodine as being of any value in the treatment of the disease, and it can be inferred that therapy involving the use of iodine has been deliberately avoided. Recently Walton (11) has written that there is a very considerable danger in giving this drug if there is the slightest evidence of hyperthyroidism. Moreover, it has frequently been found that iodides given to goitrous patients without any toxic symptoms may provoke severe symptoms of hyperthyroidism.

Against these widely accepted experiences may be set the contrary observations of Neisser (12), who in 1920 reported that he had treated cases of Graves's disease with minute doses of sodium iodide and had obtained very striking clinical improvement. The work was repeated in 1921 by Loewy and Zondek (13), who found that there was a large fall in the oxygen consumption of his patients after the administration of small doses of iodides as used by Neisser, and that their weight began rapidly to increase at the same time. Since then favourable reports of this method of treatment have been published by Beebe (14) and others in America, and by Jagić and Spengler (15) in Vienna. The point to be noticed about these results is that much smaller doses of iodine were administered than is usual in iodine therapy. The difference in the results from those usually found was doubtless due to this fact.

Independently of Neisser's work E. and M. Mellanby reported to the Physiological Society and the Association of Physicians, in 1921, that they had been making some observations on the dietetic treatment of exophthalmic goitre. They gave patients suffering from this disease such food-stuffs free from iodine as had been found to produce in growing puppies the least hyperplastic thyroids—that is, food-stuffs which would be expected to make the smallest demands on thyroid activity and possibly, in consequence, be most compatible with the reversion to normal of hyperplastic glands. At the same time iodine was given either in the form of cod-liver oil or in small doses of potassium iodide. The iodine of cod-liver oil is present in minute quantities and its action becomes evident only after some time. The early effect of giving the oil to these patients is usually to increase the metabolism and the symptoms, and to cause a loss of weight. Under this treatment the subsequent improvement in many of the cases was striking, and a rapid gain in weight, and reduction in the intensity of the nervous symptoms and tachycardia, were observed. Further experience showed that the small doses of iodine played a prominent part in effecting the alleviation of

symptoms, but it became clear that the iodine effect was complicated and that its influence varied greatly according to such circumstances, among others, as size of dose, duration of treatment, and type of case. It was decided to make a closer study of its action, and work was directed to finding out how it acted and the conditions under which its best therapeutic effect could be obtained. The results of the investigation are described below.

It is clear that an investigation of this nature has a wider interest than that dependent on its immediate or even its ultimate clinical value. It has been seen above that iodine controls largely the structure of the thyroid gland, but that the evidence that it influences metabolic processes in the body, although such processes are greatly affected by thyroid activity, is small. This situation appeared enigmatical. However, the dramatic effect of iodides in hyperthyroidism makes it clear that thyroid function as well as structure may be greatly influenced by this substance, and that the physiological action of iodine cannot be explained simply by the fact that it forms part of the active principle thyroxin. We have had in our minds throughout this work the hope of shedding further light on this relationship between iodine and thyroid activity, as well as finding out the conditions under which the best clinical results can be produced in cases of hyperthyroidism.

#### *Methods.*

Patients suffering from various types of hyperthyroidism have been kept under observation in hospital, and records of their basal metabolic rate, pulse-rate, weight, neck measurement, and general clinical condition have been made at frequent intervals. The patients received during their stay in hospital a standard diet, the energy value of which was in the neighbourhood of 1,800 calories. It was usually arranged as follows:

Breakfast: 1 egg, 3 oz. bread with jam,  $\frac{1}{2}$  pint milk.

Lunch:  $\frac{1}{2}$  pint milk.

Dinner: 2 oz. lean meat, 4 oz. potatoes, 4 oz. green vegetables, small portion of milk pudding, 1 orange.

Tea: 3 oz. bread with jam, tea with a little milk.

Supper:  $\frac{1}{2}$  pint milk.

The basal metabolic rates were determined by the Douglas bag method and the pulse-rates recorded on the accompanying charts were taken while the patients were at rest under as nearly as possible basal conditions. It should be mentioned that the conditions for obtaining 'basal' measurements were not ideal; with one exception (Case I) the samples of air had to be collected in a general ward, although by the use of screens the disturbing effect of outside influences on the patients was to some extent avoided.

Iodine was given in the form of potassium iodide. The administration was begun at varying intervals after the patients' admission, in some cases after they had been resting in hospital for six weeks or two months. The largest amount



given was 18 grains in the day, the smallest 1 grain. The effects of temporarily discontinuing the iodide and of varying the dosage were observed in many of the patients.

A brief account of the history and clinical record of eight patients follows. To each case there is appended a chart on which are recorded graphically the B.M.R., pulse-rate, and weight taken at short intervals during the period of observation.

### Case Reports.

#### Case I. Moderately severe exophthalmic goitre.

*History.* M., a nurse, aged 35, had enjoyed good health till 1916. While nursing abroad she contracted malaria and was invalidated home. She went abroad again in 1917 but did not feel really well, and towards the end of that year was again sent home. At this time she suffered from weakness, nervousness, and palpitations, and though she had no obvious enlargement of the neck she was informed that she had exophthalmic goitre. For the next

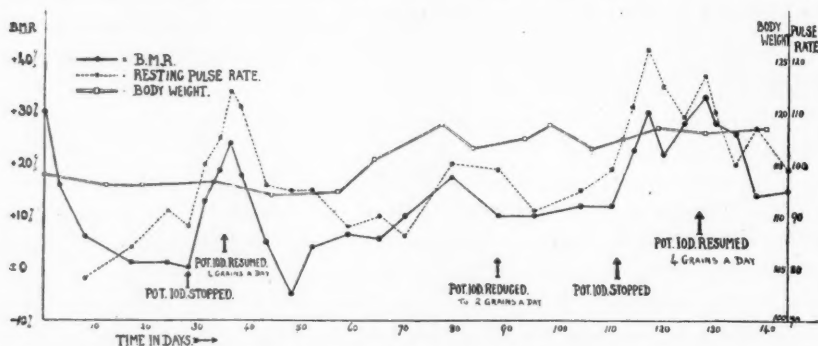


FIG. 1. Case I. Record of the B.M.R., pulse-rate, and weight. The effect of withholding iodide on two separate occasions is well shown.

three years she was able to do a little work occasionally. In 1920 her neck became obviously larger, and she was treated in hospital for six weeks with rest and X-rays. She gained considerably in weight, but remained weak and nervous. She was having a good deal of domestic worry at this time, and soon after leaving hospital became gradually worse, till towards the end of 1922 she got oedema of the legs and had to take to her bed. She was very depressed and irritable, and felt that life was a burden to her.

*Condition on admission.* Her chief complaints were of distressing palpitations and uncontrollable nervousness. She was moderately well nourished, had a slight but definite degree of exophthalmos and a moderate uniform enlargement of the thyroid. There was a fine tremor of the hands and pronounced general nervous hyperexcitability with frequent flushing and sweating of the skin. The heart was completely irregular in its action; the presence of auricular fibrillation was confirmed by electro-cardiographic records.

*Treatment.* The low calorie diet was started at once and 2 gr. of potassium iodide were given twice a day. Strict confinement to bed was ordered until very definite signs of improvement were observed. On two occasions the potassium iodide was withdrawn, once for a period of a week and a second time for a period of 16 days.

*Progress.* Detailed records of her progress are available only from the third week of treatment onwards. The accompanying chart (Fig. 1) shows the fluctuations of the B. M. R., resting pulse-rate, and weight during a period of five months. The early B. M. R. measurements were low because she had been undergoing treatment for three weeks before they were begun. The heart stopped fibrillating after one month of the régime described above, and nine months later its rhythm was still regular. It is interesting to note that on the resumption of the normal rhythm the pulse-rate fell at once to below 80, from which level it rose gradually to between 90 and 100, where it remained throughout the greater part of the period of observation. With the cessation of the fibrillation the symptoms were greatly relieved; the excessive nervousness disappeared to a large extent and the exophthalmos became less obvious, but there was no alteration in the size of her neck.

After four weeks of treatment the iodide was stopped. Within three days the B. M. R. and resting pulse-rate had risen appreciably, and at the same time the symptoms were aggravated: there was more restlessness and greater nervous excitability. At the end of a week the iodide was once more given. Three days later the pulse-rate and B. M. R. began to fall, and after ten days of iodide administration they had returned practically to their original level.

For the next two months iodide was given continuously and the B. M. R. remained fairly steady at about + 10 per cent. Reduction of the dose from four grains a day to two had no apparent effect on the patient. But when the iodide was now again discontinued altogether a distinct exaggeration of the symptoms, accompanied by a rise in the B. M. R., was again observed. After its withdrawal for 16 days iodide was again given. Ten days later the B. M. R. had fallen to approximately its former level, and an improvement in the general clinical condition was apparent.

This patient was seen four months after her discharge from hospital. She had been taking iodide continuously during this period. She was then in very fair health and had resumed her work. She had no exophthalmos and no tremor of her hands, and had gained 15 lb. in weight. There was a definite reduction in the size of her neck. The pulse was regular in rhythm, but varied from 100 to 110.

#### *Case II. Severe exophthalmic goitre.*

*History.* F. B., a single man of 25, enjoyed good health until 18 months before admission to hospital, when he began to feel worried and anxious for no particular reason, and to get attacks of nausea and vomiting. Two or three months later he noticed that his eyes were becoming prominent. He then began to suffer from frequent headaches and a 'trembling' of his limbs. His friends noticed that his mental condition was changing; he was becoming restless, emotional, and difficult to manage.

*Condition on admission.* He was pale and poorly nourished. He had a definite exophthalmos which was by no means extreme, although his eyes were not more than half closed during sleep and consequently felt sore when he awoke in the morning. The thyroid was uniformly enlarged and pulsated freely, a thrill and continuous bruit being perceptible over it. The heart was enlarged, the pulse-rate 120 and regular in rhythm. There was a fine rhythmic tremor of the hands and coarse involuntary jerky movements of the whole limbs occurred from time to time. He was excitable, restless, and suspicious; he slept badly, and would sometimes start up at night as though about to attack his neighbours in the ward.

*Treatment.* Five days after his admission he was given 2 gr. of potassium iodide twice a day. This dose was kept constant for five weeks, and during the following nine weeks was increased, first to 3 gr. twice a day, then to 6 gr. twice a day, and finally to 6 gr. three times a day. After this large dose had been given for a fortnight the iodide was discontinued altogether for 16 days, and was then resumed in doses of 2 gr. twice a day. The iodide was now given continuously

for a period of four months, and was then once more discontinued for a fortnight, after which it was resumed.

*Progress.* During the first month his B. M. R. fell steadily from + 70 per cent. to between + 20 per cent. and + 30 per cent., his clinical condition improving at the same time. The B. M. R. then rose suddenly to + 50 per cent., at which level it remained for a week, and then settled down to a fairly constant value of about

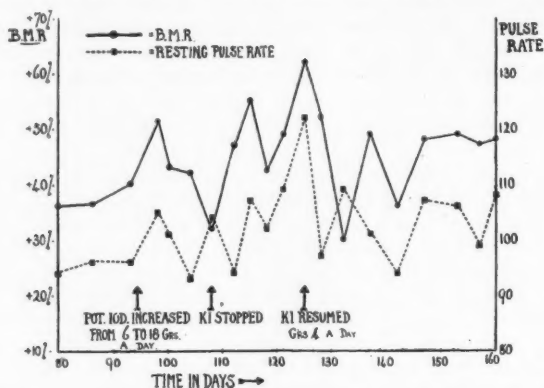


FIG. 2. Case II. The patient had been receiving large doses of iodide and showed severe symptoms at the beginning of the period illustrated here. The condition became worse, as is shown by a further rise in the B. M. R., when the iodide was stopped.

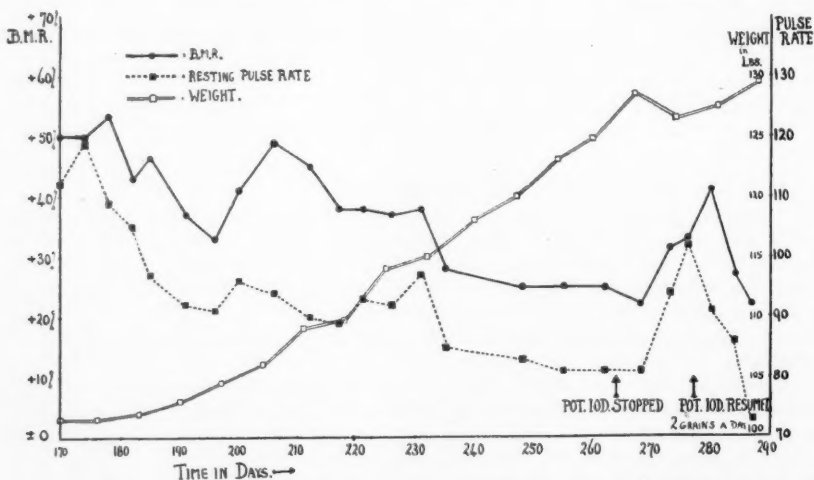


FIG. 3. Case II. A record of the same patient as Fig. 2, at a later period. During the greater part of this time he was receiving 1 gr. of iodide a day. The effect of stopping the iodide after its administration for nine months is seen.

+ 40 per cent., which was maintained for the next six weeks. During this period of six weeks the dose of iodide was increased on three occasions. The effect of raising the dose was on the last two occasions to cause an exaggeration of the nervous symptoms, which became apparent two or three days after the increased amount was given, but lasted only for a few days. This was particularly noticed when the large dose of 18 gr. a day was given: the symptoms became as severe, both subjectively and objectively, as they had been at the commencement



of treatment, and were accompanied by a transient rise of the B. M. R. After three or four days, however, he seemed to accommodate himself to the increased dose of iodide and the symptoms improved.

At this stage we decided to omit the iodide altogether. The result was a further exaggeration of the symptoms and a rise in the B. M. R. The iodide was withheld for 16 days and then recommenced in doses of 2 gr. twice a day. The resumption of the iodide was followed by an improvement in his condition and a transient lowering of the B. M. R., but the latter soon rose again and settled down to a constant level of about + 50 per cent., where it remained for the next month, being unaffected by a reduction of the iodide from 4 gr. a day to 2 gr.

He had now been in hospital for four months; he was still very nervous and excitable, his pulse was rapid and his heart tumultuous in its action. His weight had at one time been slowly rising, but for the last month had been steadily falling. His goitre, however, was diminishing in size; the neck measurement had been  $14\frac{1}{2}$  in. on admission and was now only  $13\frac{1}{2}$  in. A remarkable improvement now began to take place. The B. M. R. and pulse-rate fell steadily and the weight increased. This improvement was watched for three months, during the whole of which time he was receiving 2 gr. of iodide a day. At the end of this time his B. M. R. was + 25 per cent., his resting pulse-rate 80, and he had gained 27 lb. Iodide had been given altogether for 37 weeks and it was now stopped, medicine not containing iodide being substituted to eliminate any possible effect of suggestion. For the first few days there was no change in his condition; then he began to complain of palpitations and disturbed sleep, and his pulse-rate and B. M. R. rose. His weight, which had been rising steadily for three months, began to fall. The iodide was withheld for 13 days and then resumed. Its resumption was very soon followed by a marked improvement in the symptoms and a rise in weight. Within 10 days the B. M. R. had fallen to + 20 per cent. and a resting pulse of normal frequency was observed for the first time.

### *Case III. Severe exophthalmic goitre.*

*History.* M. H., a single girl of 19, had 'always had rather a big neck', but took no notice of it till two years before admission to hospital, when it increased in size and she consulted her doctor about it. She felt quite well at this time and paid no further attention to the swelling of her neck till 18 months later, when she began to get short of breath and to suffer from frequent headaches. She then received a course of X-ray treatment which she states did not do her very much good. She had spent a month in bed shortly before coming into hospital, and had recently had a bout of vomiting which lasted a week.

*Condition on admission.* She was poorly nourished and very restless and excitable. She perspired freely and flushed deeply at the slightest provocation. She had pronounced exophthalmos with a well-marked von Graefe's sign. The thyroid was very considerably enlarged but was not pulsating: the swelling was uniform and of firm consistence. The heart's apex-beat was displaced somewhat to the left. The pulse-rate was 140, the rhythm was regular, and its wave was distinctly of the collapsing type. There was no rhythmic tremor of the hands, although coarse jerky movements were apparent in the arms when an attempt was made to hold them out steadily.

*Treatment.* 2 gr. of potassium iodide were given twice a day after she had been under observation for a week. This dose was continued for two months and then reduced to 1 gr. twice a day. Six weeks later the drug was stopped altogether, but was resumed after eight days and kept on till her discharge.

*Progress.* It will be seen from the chart (Fig. 4) that the B. M. R. and resting pulse-rate were very considerably raised during the 10 days immediately following her admission. They showed a sudden fall 8 days after the iodide was begun, the pulse-rate dropping from 120 to 90 and the B. M. R. from + 65 per cent.

to + 20 per cent. This low level was maintained for three or four weeks and was accompanied by a marked improvement in the nervous symptoms. After this period both the B. M. R. and pulse-rate began slowly to rise, the B. M. R. reaching a level of about + 30 per cent. During this time her weight was increasing fairly steadily and her general condition was good. After the iodide had been given for four months it was withdrawn completely. Within a week there was a very noticeable return of the nervous symptoms; the B. M. R. was raised to + 60 per cent. and the pulse-rate to 136, and her weight began to fall. The iodide was resumed when it had been withheld for eight days. Its resumption was soon followed by an improvement in the general condition and a fall in the B. M. R.

During the 20 weeks of her stay in hospital she gained 25 lb. in weight. Her exophthalmos diminished a great deal, but her neck measurement increased by one inch and the thyroid was harder than at the time of her admission.

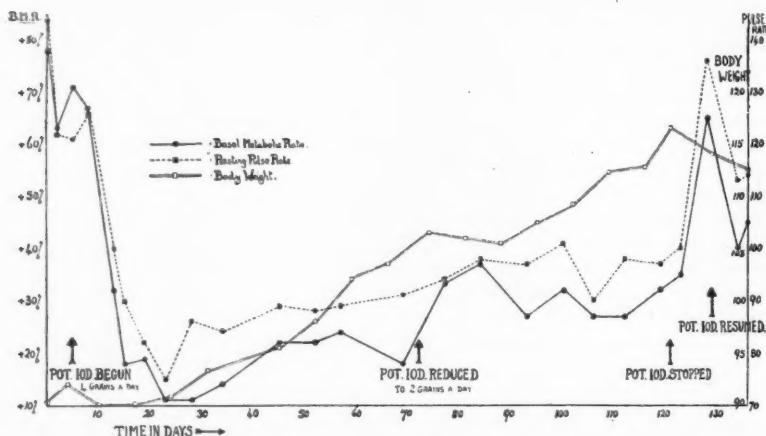


FIG. 4. Case III. The pronounced fall in the B. M. R. and pulse-rate during the first three or four weeks of the iodide administration is succeeded by a gradual rise. Withdrawal of the iodide after four months is quickly followed by a considerable rise in the B. M. R., accompanied by a fall in weight.

#### Case IV. Moderately severe exophthalmic goitre.

*History.* L. F., a married woman of 38, had enjoyed very good health until two years before coming under observation. At this time she was very much upset by the loss of one of her children and soon became thoroughly 'run down'. She got short of breath and felt tired out as soon as she started to do her work. She did not lose her appetite, but, in spite of eating more than she had been accustomed to eat, she lost a good deal of flesh. Some eighteen months after the onset of the symptoms she noticed that her neck was getting larger. Of late she had been getting worse and had had several bouts of vomiting lasting two or three days. She had not laid up in bed on account of her condition.

*Condition on admission.* She was poorly nourished, restless, and very excitable. She had a slight degree of exophthalmos, but no von Graefe's sign. The thyroid was uniformly enlarged to a moderate degree. The outstretched hands exhibited a fine tremor and the pulse-rate ranged between 100 and 120. The heart was regular in its action and did not seem to be enlarged.

*Treatment.* She was kept in bed for five weeks on the usual diet and given no other form of treatment. At the end of this period she was given two grains of potassium iodide a day, and this dose was continued for two weeks, when she left the hospital.

**Progress.** Two days after admission the B. M. R. was + 67 per cent. and the resting pulse-rate 125. Both the B. M. R. and pulse-rate fell steadily until at the end of three weeks the former was + 30 per cent. and the latter round about 90 (Fig. 5). At the same time there was a marked improvement in the symptoms, and the patient's weight, which had fallen very appreciably during the first week, began steadily to go up. During the next two or three weeks the B. M. R. remained in the neighbourhood of + 40 per cent., although the weight continued to rise and the pulse-rate to fall. Five days after the administration of potassium iodide had been begun the B. M. R. had fallen to + 17 per cent., and four days later was + 7 per cent., the resting pulse-rate being below 70. She was discharged from hospital after having taken the iodide for just over a fortnight. She had lost her tremor and her excessive nervousness, could take moderate exercise without feeling any shortness of breath or palpitations, and felt better than she had done for many months. There was no alteration in the size of her neck during her stay in hospital.

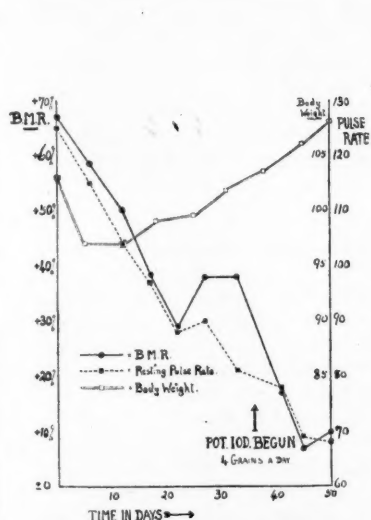


Fig. 5. Case IV. The patient had been resting in bed without medicine for five weeks before iodide was given. The B. M. R. fell considerably during this time, but a further rapid fall followed the giving of iodide.

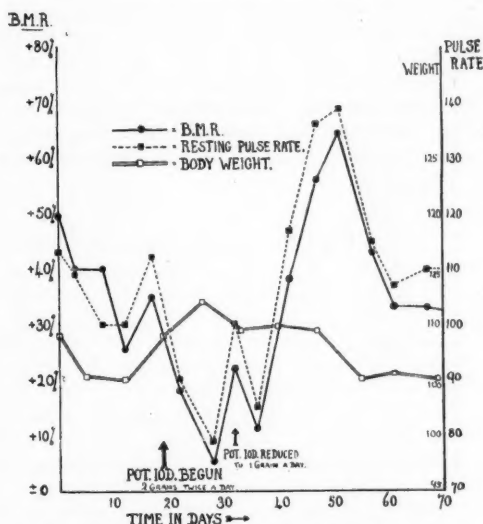


Fig. 6. Case V. The giving of iodide is followed by a considerable fall of the B. M. R. The low level is not maintained and is quickly succeeded by a rise to a higher point than it had ever reached before.

#### Case V. Moderately severe exophthalmic goitre.

**History.** E. H., a married woman of 34, had been ailing for three years. She was troubled with frequent headaches and a constant sense of fatigue, and of late had been short of breath after slight exertion. She had noticed a swelling of her neck for a considerable time, but had not paid much attention to it. She had recently been receiving a course of arsenical injections, but her Wassermann reaction on admission to hospital was negative.

**Condition on admission.** She was moderately well nourished, had a slight degree of exophthalmos and a pronounced tremor of her hands. There was a diffuse enlargement of the thyroid, which felt soft and pulsated. Her heart was somewhat enlarged and her pulse-rate varied between 120 and 130. She exhibited a moderate degree of nervous hyperexcitability.

**Treatment.** She was kept at rest in bed for three weeks without medicine,

and then given two grains of potassium iodide twice a day for a fortnight. The iodide was then reduced to one grain a day.

*Progress.* During the first three weeks her B. M. R. varied between + 40 per cent. and + 25 per cent. (Fig. 6). She showed some signs of improvement towards the end of this period, but her pulse-rate had not fallen appreciably. Ten days after the commencement of the iodide there was a very marked general improvement. The B. M. R. had fallen almost to the normal level and the pulse-rate was below 80. She felt better than at any time during the past two years. This state of things did not last more than two or three days. Her thyroid then began to swell and became hard and tender. Pulsation in the gland had previously disappeared and now returned with greater intensity than before. The pulse-rate and B. M. R. quickly rose and her weight began to fall. At this point the iodide was reduced from four grains a day to one grain, but the reduction did not seem to influence the course of this 'reaction', which reached its maximum severity one month after the beginning of the iodide administration.

She now began to improve again, and the B. M. R. fell from the high level of + 65 per cent. which it had reached to the neighbourhood of + 30 per cent., where it remained for the next three weeks. During these three weeks the thyroid became softer and its pulsation disappeared, but it was not appreciably reduced in size. She left the hospital in much the same state as when she came in. She had lost two or three pounds in weight and was still excitable and had a rapid pulse. Her neck measurement had increased from  $13\frac{1}{2}$  inches to  $14\frac{1}{2}$  inches.

*Case VI.* Moderately severe hyperthyroidism without exophthalmos.

B. H., a single girl of 22, had noticed a swelling of her neck for nine years. She had felt perfectly well until she had an attack of scarlet fever eighteen months before admission to hospital. From this time onwards she found some difficulty in coping with her work, began to get severe headaches, and to suffer from shortness of breath and palpitations. Her work was very strenuous, but she had no particular cause for worry of any kind. She had a sister with a goitre, but this had never given any trouble and is said to have been 'cured'.

*Condition on admission.* She was well nourished, had a very considerable enlargement of her neck, but no suggestion of exophthalmos. She was excitable and suffered from vasomotor instability, as evidenced by frequent flushing and sweating of the skin. There was a fine rhythmic tremor of the hands and the pulse-rate varied from 120 to 150. There was a general enlargement of the thyroid and a small nodule could be felt in the left lobe; no pulsation could be felt in the gland. The heart appeared to be normal in size and was regular in its action.

*Treatment.* For five weeks she was kept in bed and given the fat-restricted diet; no other treatment was given during this period. Potassium iodide was then given in doses of two grains twice a day and continued for seven weeks until her discharge from hospital.

*Progress.* During the first ten days she was under observation, the B. M. R. fell from + 63 per cent. to + 23 per cent. and the pulse-rate from 120 to 90. She became less excitable and subjectively felt a distinct improvement, but was still troubled with frequent severe headaches. The B. M. R. then rose a little and for the next three weeks kept in the neighbourhood of + 30 per cent., while there was a corresponding rise in the resting pulse-rate. After the administration of potassium iodide had been started there was no immediate change in the clinical condition of the patient, although during the first week there was a distinct rise in the B. M. R. This preliminary rise was succeeded by a fall to a distinctly lower level than had been reached previously, and at the same time there was further improvement in the general symptoms, including the dis-

appearance of the headaches. The B. M. R. was on one occasion as low as +5 per cent. (Fig. 7), but it fluctuated a good deal and at the patient's discharge was +20 per cent. The resting pulse-rate varied during this time between 90 and 100. During her stay in hospital there was a noticeable alteration in the size of the thyroid. On admission the circumference of the neck measured  $14\frac{1}{2}$  inches; when the potassium iodide was begun it was 14 inches, and at the time of her discharge it was  $13\frac{1}{2}$  inches. The body-weight kept fairly steady during the whole period of observation.

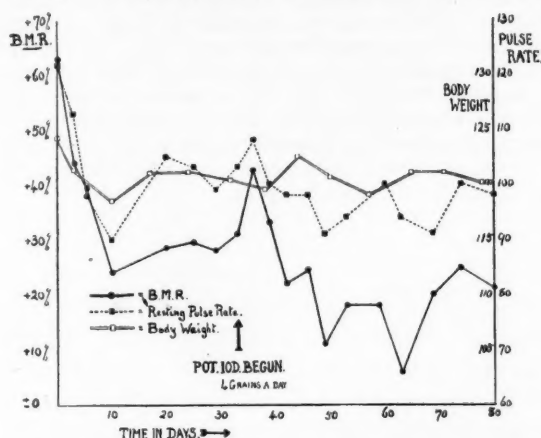


FIG. 7. Case VI. Iodide treatment was not begun till the patient had been resting for five weeks. It was followed by a definite fall in the B. M. R., although the pulse-rate was not greatly affected.

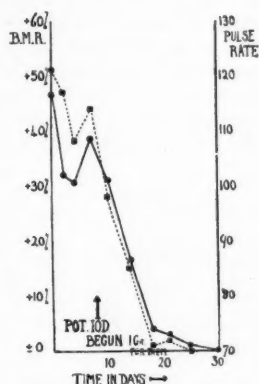


FIG. 8. Case VII. The B. M. R. reached the normal level ten days after the commencement of iodide administration. There is a very striking parallelism between the curves of the B. M. R. and pulse-rate.

#### Case VII. Mild hyperthyroidism without exophthalmos.

**History.** S. P., a clerk aged 32, complained of palpitations and nervousness which had troubled him for many years and which had become worse a few weeks before his coming into hospital. The palpitations were brought on more by excitement than by exertion, and were often accompanied by a tremor which temporarily prevented his continuing his work. He had been losing weight for the last year or two and had noticed a slight swelling of his neck.

**Condition on admission.** He appeared thin in the face, but was otherwise moderately well nourished. There was no definite exophthalmos, although the eyes were a trifle staring. There was a slight uniform enlargement of the thyroid, which showed no pulsation. The heart's apex beat was in the nipple line and the pulse-rate ranged from 110 to 120. There was occasionally a fine tremor of the hands.

**Treatment.** One-half of a grain of iodide was given twice a day, after eight days of observation, during which he was kept at rest in bed and fed on the special diet.

**Progress.** Before the iodide was begun the B. M. R. readings varied between +30 per cent. and +40 per cent. Five or six days after its administration there was an obvious improvement in the clinical condition and both the pulse-rate and the B. M. R. had fallen considerably. By the end of a fortnight the pulse-rate and B. M. R. had reached the normal level (Fig. 8) and the patient felt better than he had done for many years. The improved condition lasted



throughout the next three weeks, when an acute tonsillitis supervened. Two days after the subsidence of the fever the pulse-rate and B.M.R. were both somewhat raised, but at this stage he left the hospital, so that we were unable to determine whether the rise were a transient one due to the febrile attack or whether it represented the 'reaction' that has been observed in the majority of patients treated with iodides.

*Case VIII. Hyperthyroidism without goitre.*

*History.* A. W., a single girl of 21, was admitted to hospital with an acute pericarditis following pneumonia. She had some irregular pyrexia for three weeks, at the end of which time the pericarditis had apparently cleared up, leaving her emaciated, anaemic, and with a very rapid pulse. She was kept under observation for two months, during which she appeared to make no progress. She was extremely nervous and excitable, and her pulse was sometimes so rapid as to be almost uncountable. It was thought possible that her symptoms might be attributable to hyperthyroidism, and she was handed over to our care so that observations on this point might be made.

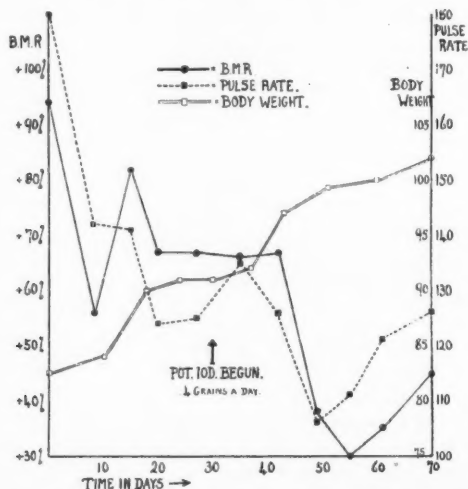


FIG. 9. Case VIII. It will be seen by examination of the weight-curve that this patient was improving during the four weeks preceding the iodide administration. There was a very considerable drop in the B.M.R. and pulse-rate between two and three weeks after the commencement of the iodide, but the comparatively low level reached at this stage was not well maintained.

*Condition at the time the present observations were begun.* She was pale and emaciated, weighing but 5 st. 12 lb. She was restless and excitable and had a well-marked tremor of her hands and lips. The heart was considerably enlarged, but there was no evidence of any valvular lesion. The thyroid was difficult to feel, and in fact seemed smaller than usual for a girl of her age. There was no suggestion of exophthalmos.

*Treatment.* She was kept on the diet for one month and was then given two grains of potassium iodide twice a day. This dose was kept up for the next six weeks until she left hospital. She was kept in bed at the beginning of the treatment, but as her general condition improved she was allowed to get up and take mild exercise.

*Progress.* She was so very excitable at first that it was found impossible to obtain consistent figures for her B.M.R. Thus during the first three weeks

she was under observation the measurements fluctuated between +94 per cent. and +56 per cent. After this she began to show definite signs of improvement, and although the B. M. R. kept steady at the high level of +67 per cent., her weight slowly increased. The potassium iodide was started when the B. M. R. appeared to be more or less constant. There was no apparent effect on either the B. M. R. or pulse-rate for the first twelve days of its administration. There was then a fall in the B. M. R. of nearly 30 per cent., while the resting pulse-rate fell from 126 to 106. The fall in the B. M. R. was continued for a week, and a gradual rise then took place, so that on her discharge from hospital the B. M. R. was +45 per cent. (Fig. 9).

During the ten weeks of treatment outlined above she gained 20 lb. in weight and lost much of her excessive nervousness. Her pulse-rate remained high, although she could take mild exercise without causing herself any distress. It is interesting to note that the circumference of her neck increased out of proportion to her general increase of flesh, and her thyroid could be very readily felt when she left hospital.

#### *Discussion of results.*

In every case of hyperthyroidism that we have observed up to the present time the giving of small doses of iodide has resulted in a distinct clinical improvement. This improvement becomes obvious at the end of a week, and as regards slowing of the pulse-rate, lowering of the B. M. R., and lessening of the general nervous excitability, attains a maximum between the tenth and the twentieth days of the treatment. From this time onwards we have observed considerable variation in the response of different patients. (1) They may remain for several weeks in this improved condition, with a low B. M. R. and slow resting pulse-rate, and then develop a slight and gradual return of the symptoms. (2) There may be a rather sudden return of the symptoms soon after their maximum decline, the patients continuing to put on weight and regain strength in spite of an increased metabolism and tachycardia. These two classes comprise the bulk of the patients that we have observed. (3) Occasionally there may be a more violent exacerbation in which the symptoms return within the course of a week or two to their original degree of severity. A striking example of this type of response was obtained in a patient whose case has not been detailed above. She had a large adenomatous thyroid of long standing with severe toxic symptoms. After four days of iodide treatment her B. M. R. fell from +55 per cent. to +8 per cent. with corresponding clinical improvement. The B. M. R. remained at this level for a fortnight and then rose quickly to its former level.

We are not able to predict with any certainty what course is likely to be followed by any particular case. It would appear, however, that those patients with large hard glands are more likely to develop severe 'reaction' symptoms than those with smaller soft ones.

The amount of iodide given does not appear, within certain limits, to control the rate of improvement noted in the early stages of treatment. Thus the giving of nine grains of potassium iodide a day has been followed by the same

rapid improvement that has been observed when one grain was given. We believe that when very small doses are given the return of symptoms tends to be longer delayed and less severe than when larger doses are given. We have not yet determined the minimum quantity of iodide that will exert a demonstrable effect, but it is less than half a grain a day. When a return of symptoms has occurred while the patient was receiving a comparatively small dose of iodide, no improvement has been found to follow the reduction of the dose; on the other hand, increasing the dose under these conditions has in our experience caused a still further exaggeration of the symptoms.

Withdrawal of the iodide has always been followed by an increase in the severity of the symptoms. Thus in Case II iodide had been given for nine months and the goitre had practically disappeared, yet when the iodide was stopped there was within a week a return of the tachycardia, an increase in the B. M. R., and a loss of weight. Resumption of the iodide has invariably been followed by a rapid return to the state that existed before the withdrawal.

We are unable to make any detailed statement concerning the effect of iodides on the structure of the thyroids in these cases, as we have obtained no material for histological study either from the post-mortem room or the operating theatre. Not uncommonly the glands become larger and firmer during the first few weeks of treatment. Pulsation in the glands diminishes in all cases and as a rule disappears after two or three weeks. In some cases there is subsequently a slow but steady diminution in the size of the goitre. During the more severe exacerbations the gland may increase in size and show signs of increased vascularity, but this change is not constant.

The aggravation of the symptoms that follows the withdrawal of the iodide even after many months of continuous administration lends some support to the suggestion mentioned in the introduction, that some factor may be at work which causes iodine to be withdrawn rapidly from the thyroid, thus allowing it again to become hyperplastic. It is possible that the presence of a certain quantity of iodine in the gland suppresses its activity to a maximum extent, but that the presence of more or less upsets the balance and allows an exaggeration of the symptoms to take place.

Examination of the figures shows that a considerable increase in weight is commonly observed while the patients are receiving iodide. This increase may occur while B. M. R. is as high as + 30 per cent. or even + 40 per cent., in spite of the comparatively low energy value of the diet.

After many months of treatment with small doses of iodide most of the patients retain to some degree their excessive nervous reaction to unwonted stimuli. This is seen particularly in those who have been discharged from hospital and attend as out-patients. They may present themselves with a rapid pulse and a tremor which they state they do not notice while they are engaged in their usual occupations.

In general it would appear that the mode of response of these patients to iodide therapy is remarkably similar to that observed to follow surgical treat-



ment. Similar periods of 'primary improvement' and 'relapse' described by Walton (16) as recognizable in all cases of exophthalmic goitre treated by surgical means have been illustrated in the above series of cases.

From the practical point of view we believe that the giving of small amounts of iodide to patients suffering from hyperthyroidism is a valuable adjunct to other medical treatment, and it is possible that doses of the order of  $\frac{1}{10}$  grain daily will prove to be the most suitable for the majority of cases. We have no grounds for considering this treatment as a curative one. It may prove useful as a preliminary measure in cases where surgical operation is considered advisable. Marine and Lenhart (9) found that in those cases which best withstood operative treatment the iodine content of the thyroids was higher than in the cases which showed severe post-operative disturbances, and put forward the view in 1911 that operations on these cases should not be undertaken until the thyroid had returned to its colloid state either spontaneously or by the action of minute doses of iodine.

From the standpoint of the physiology of the subject we are not yet in a position to discuss the bearing of these results on the part played by iodine in metabolism, apart from the fact that it is a constituent element of thyroxin. It seems certain, however, that iodine influences metabolic change in ways not at present understood.

#### *Summary.*

The relationship between the iodine content of the thyroid gland and the occurrence of the symptoms of hyperthyroidism in man is discussed. Small doses of iodides are shown to produce a lowering of the basal metabolic rate and distinct clinical improvement in patients suffering from hyperthyroidism. As regards the immediate results, this improvement reaches a maximum in from 10 to 20 days after the beginning of iodide administration, and is then frequently followed by a gradual return of the symptoms, which do not as a rule attain their former severity. The withdrawal of iodide from patients who have been receiving it continuously for several months is followed by an exacerbation of symptoms which can be relieved by once more administering iodide. Treatment by iodides of cases of hyperthyroidism of all types is recommended as an adjunct to other forms of medical treatment, and it is suggested that a course of iodide administration should prove of value as a preliminary to any surgical treatment of these cases that may be contemplated.

This investigation was carried out on behalf of the Medical Research Council, to whom our thanks are due.

## REFERENCES.

1. Marine, D., and Lenhart, C. H., *Arch. Int. Med.*, Chicago, 1909, iv. 253.
2. Marine, D., *Journ. Exp. Med.*, New York, 1914, xix. 376.
3. Marine, D., and Kimball, O. P., *Arch. Int. Med.*, Chicago, 1920, xxv. 661.
4. Plummer, H. S., *Journ. Amer. Med. Assoc.*, 1912, lix. 327-8.
5. Marine, D., *ibid.*, 1912, lix. 325.
6. MacCallum, W. G., *ibid.*, 1912, lix. 328; 1907, xlix. 1158.
7. Virchow, R., *Die krankhaften Geschwülste*, Berlin, 1863, iii, i. 74.
8. Mayo, C. H., *Journ. Amer. Med. Assoc.*, 1912, lix. 327.
9. Marine, D., and Lenhart, C. H., *Arch. Int. Med.*, Chicago, 1911, viii. 316.
10. Kocher, T., *Arch. f. klin. Chir.*, Berlin, 1910, xcii. 1166.
11. Walton, A. J., *Lancet*, Lond., 1923, ii. 58.
12. Neisser, E., *Berl. klin. Wochenschr.*, 1920, lviii. 461.
13. Loewy and Zondek, *Deutsch. med. Wochenschr.*, 1921, xlvii. 1387.
14. Beebe, S. P., *Med. Rec.*, New York, 1922, ci. 135.
15. Jagić, N., and Spengler, G., *Wien. klin. Wochenschr.*, 1923, xxxvi. 264.
16. Walton, A. J., *Lancet*, Lond., 1923, ii. 272.

## A CLINICAL STUDY OF VAN DEN BERGH'S TEST IN JAUNDICE

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### *Introduction.*

A GREAT impetus has been given in recent years to the study of jaundice by Hymans van den Bergh. This worker (13, 14) has successfully applied Ehrlich's diazo-reaction to the quantitative estimation of bilirubin in the serum and other body fluids. He believes, moreover, that by the application of this test it is possible to distinguish between obstructive and haemolytic jaundice. If this be the fact, a useful weapon for attacking the problems of jaundice is at hand.

Van den Bergh's test has by now been employed by numerous workers in this country. As far as the writer is aware, however, no considerable series of cases has been published in English. A number of workers, both here and abroad, have met with apparently discordant results and consequently seem to be in some doubt as to the value of the test. It is in the hope of throwing some light on this question that this paper is brought forward.

Recent work on the pathology of jaundice, the principles underlying van den Bergh's test, and the actual technique of the test have been so recently described in this Journal by McNee (10) that it is unnecessary to enter into them in any detail. Nor is it proposed to discuss the advantages of this test over rival methods for the clinical estimation of the amount of bilirubin in the blood-serum: they are by now fairly established. The principle of the test is this: bilirubin reacts with Ehrlich's diazo-reagent in neutral or acid solution to give a red colour; this is due to azo-bilirubin. The reaction may occur at once (within thirty seconds), in which case it is said to be direct; or the colour may only develop gradually in aqueous solution (delayed reaction), but a pinkish violet colour appear promptly in alcoholic solution (indirect reaction). All sera giving a direct reaction will give also the indirect reaction.

It is suggested by van den Bergh that bilirubin may exist in the serum in two forms, differing perhaps only in their physical condition, and that the direct reaction is positive or negative according to the form in which the bilirubin is

A third type of reaction is described, in which a pink colour begins to appear within half a minute and very gradually deepens. Such a change constitutes what is known as a 'biphasic' reaction, and it is thought to be due to a mixture of the 'direct' and 'indirect' forms of bilirubin in the serum.

In performing the direct test McNee takes as his criterion a red colour that is maximal in 30 seconds. I have hardly ever found such a reaction, and even with fresh bile the colour goes on developing after 30 seconds. If a red colour begins to appear within 30 seconds I consider that the direct reaction is positive.

Van den Bergh's test can be applied quantitatively by comparing the pink colour of azo-bilirubin obtained in performing the indirect test with a standard in a colorimeter. Van den Bergh used at first a standard azo-bilirubin solution, but later an ethereal solution of iron sulphocyanide. The results are expressed as units of bilirubin. One unit is arbitrarily taken as one part of bilirubin in 200,000. Normal human serum contains from 0.2 to 0.6 units.

#### *General Results obtained by the Test.*

Van den Bergh and others have found that fresh bile gives a direct reaction; so does serum from cases of obstructive jaundice. On the other hand, normal sera, sera from cases of haemolytic jaundice, and the locally formed bilirubin (or haematoidin) in haemorrhagic exudates give the indirect reaction only. These facts have led some observers (14) to the hypothesis that bilirubin formed extrahepatically, or perhaps by the Kupffer cells, gives an indirect reaction and that the pigment is modified in the course of excretion by the liver-cells, so that it gives a direct reaction in the bile, if excreted, or in the serum, if reabsorbed into the blood-stream, in obstructive jaundice. Besides obstruction and haemolysis, a third cause for jaundice is admitted by nearly all modern writers—damage to the function of liver-cells. This form of icterus is classed by van den Bergh with haemolytic jaundice under the name of dynamic (as opposed to mechanical) jaundice, and it is usually said to give an indirect, or a biphasic reaction. The matter will be discussed more fully farther on.

In undertaking a clinical study of van den Bergh's test, it was necessary to consider the following points:

(i) Has van den Bergh's test any clinical value as a means of differentiating jaundice due to obstruction from that due to liver-cell damage or haemolysis? In particular, is the test of value in distinguishing between catarrhal jaundice and cholelithiasis? There has been an impression in this country that the test would be of great clinical value in this direction.

(ii) Is the test of value for any other clinical purpose?

(iii) Does the test throw any light on the circumstances under which bilirubin is excreted into the urine?

*Personal Results.*

My own clinical material includes 184 cases, which are tabulated below except for a few in which the diagnosis remained quite obscure; for this reason they were perforce ruled out of account. The tables state the age and sex of the patient, the diagnosis, the foundation on which the diagnosis rests (whether autopsy, operation, or clinical observation), the degree of jaundice, the occurrence or otherwise of bilirubinuria, and any data or comments which appear relevant.

The amount of bilirubin present in the serum is stated. While this was usually estimated after performing the indirect test as described above, it is also possible to estimate the colour obtained in performing the direct test, though frequently the colour so obtained is too yellowish for accurate comparison with the standard. It will be seen in the tables below that in many cases estimations have been made in both ways on one specimen of serum, and that there is a discrepancy between the two results; this is because a considerable part of the bilirubin present under certain conditions tends to be adsorbed to the protein which is precipitated in performing the indirect test, thus causing a low value to be obtained when this method is used for quantitative measurement. This adsorption of bilirubin to the protein precipitate is a serious obstacle to accurate measurements. It was observed by van den Bergh himself, who noted that it occurred with the direct far more than with the indirect form of bilirubin.

A. *Cases of frankly obstructive jaundice.* It will be seen that in cases of obstruction from gall-stones, carcinoma of the head of the pancreas and the like, or trauma, van den Bergh's test invariably gave a direct reaction. The results were consistent and bear out the results of other workers. Only one reservation must be made: the fact has been recorded clinically (8, 11, 14) that at the very onset of obstructive jaundice due to cholelithiasis, as also when it is fading, the serum may go through a stage when it gives a biphasic or even an indirect reaction, the amount of bilirubin in the blood being at the time quite low. This has been attributed, but without proof, to the presence of a bile-pigment disturbance consequent on damage to the liver-cells, which occurs earlier and persists later than the far more conspicuous disturbances due to gross obstruction.

TABLE I. *Cholelithiasis.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
1	F	66	+	17.7	++	+	op.	
2	M	71	+	+	++	+	op.	
3	M	70	1.5 (biphasic)	+	++	?0	op. & P.M.	2 days after operation
4	F	34	11.1	+	++	+	clin.	
5	M	67	+	3	+	?0	op.	

TABLE II. *Carcinoma of Head of Pancreas, &c.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
6	M	62	7.4	6.5	++	+	} op. & P.M.	New growth of common duct
		3 weeks later	14	+	++	+		
7	F	42	+	16	++	+	op.	
8	F	56	20	+	++	+	clin.	
9	F	51	13	15	++	+	} op.	
		3 weeks later	4	4	+	+		
			(biphasic)					

TABLE III. *Other Obstructive Jaundice.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
10	F	47	2+	1.5	+	0	} clin.	Jaundice following cholecystectomy. Traumatic? Ultimately cleared up
		8 days later	17	13.3	+	+		
		14 days later	3.6	+	+	+		
11	M	38	+	6.5	+	+	P.M.	Cholecystitis. Large gland against common duct
12	F	64	10	+	+	+	P.M.	Obstruction? traumatic. Dilated ducts behind a ? ligature in portal fissure

TABLE IV. *New Growth of Liver.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
13	M	44	0	0.5	0	0	P.M.	Primary carcinoma of pylorus
14	M	56	+	12	++	+	clin.	Multiple growths
15	M	52	28	21	++	+	clin.	
16	M	24	? 0	1.5	0	0	} op.	
17	3 days later		+	1	0	0		
	M	45	0	0.9	0	0	} P.M.	
3 weeks later		3.5	3	+	0			
18	M	68	2 (biphasic)	1.6	+	0	P.M.	Multiple growths
19	M	66	18 (biphasic)	16	++	+	P.M.	Possibly tumour in common bile duct region
20	F	33	13	13	++	+	clin.	
21	M	38	0	1	0	0	P.M.	Multiple growths

The results in cases of new growth of the liver are less uniform. There may be no jaundice, and there may, as in Case 13, be a normal bilirubin content of the serum. More often, however, as in Cases 16, 17, and 21, van den Bergh's test reveals a 'latent' jaundice. When there was tissue icterus a direct reaction was invariably seen in the cases tabulated. The indirect reaction found in some of the cases with latent jaundice may perhaps be the result of a liver damage



factor and analogous in its causation to the indirect reaction mentioned above as met with at the onset of obstructive jaundice due to gall-stones.

*B. Cases of frankly haemolytic jaundice.*

TABLE V. *Acholuric Jaundice.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
22	M	c. 30	0	1.5	0	0	op.	Spleen removed some years before. Complicated by a meningococcal meningitis
6 weeks later			0	0.5	0	0		After recovery from meningitis
23	F	c. 40	0	8.5	(+)	0	clin.	Sister of No. 22
24	F	c. 45	0	2.5	(+)	0	clin.	Acquired acholuric jaundice
25	M	11	0	0.6	0	0	op.	Splenectomy three years ago

TABLE VI. *Paroxysmal Haemoglobinuria.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
26	F	?	0	0.8	0	0	clin.	No haemoglobinuria for previous week

TABLE VII. *Pernicious Anaemia.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
27	M	46	0	2.5	+	0	clin.	R. B. C. 445,000
28	M	62	0	5	+	0	clin.	R. B. C. 1,250,000
29	M	55	0	3.75	+	0	clin.	R. B. C. 2,000,000
30	M	47	0	5	+	0	P.M.	R. B. C. 2,500,000
1 month later			0	1	+	0		
31	M	58	0	1.3	+	0	clin.	R. B. C. 1,800,000
32	M	48	0	0.9	0	0	clin.	R. B. C. 3,350,000. Colour index=1. Possibly a secondary anaemia
33	M	52	0	2.3	+	0	clin.	R. B. C. 1,300,000
34	M	47	0	1.5	0	0	clin.	R. B. C. 1,700,000
8 days later			0	1.5	0	0		R. B. C. 1,900,000
31 days later			0	3.7	+	0		R. B. C. 3,700,000.
36 days later			0	2.0	+	0		Febrile attack
49 days later			0	0.85	0	0		R. B. C. 2,600,000
64 days later			0	0.6	0	0		R. B. C. 3,600,000
35	M	50	0	0.75	+	0	clin.	R. B. C. 4,400,000
36	F	48	0	3.7	+	0	clin.	R. B. C. 1,300,000
								R. B. C. 1,720,000

The results in the cases of haemolytic jaundice are again consistent. The above figures confirm the results of others (8, 14) in that an indirect reaction only is encountered. Whenever there is tissue jaundice the bilirubinaemia is above normal. The series of pernicious anaemia cases illustrates one of the most

important clinical uses of the test—in distinguishing a haemolytic anaemia from one due to other causes. It is true that the presence of urobilin in the urine will throw light on this point. Van den Bergh's test, however, appears to be a more sensitive indicator; in several instances it gave a reading above normal when there was no abnormal urobilinuria. Case 34 is of special interest. The patient was moderately anaemic when first seen and gradually improved. One day he developed an acute febrile illness resembling influenza; his blood-count fell rapidly and the bilirubin value of his blood rose considerably. At the same time he became obviously jaundiced. His fever lasted only a few days; his blood-count rose and his bilirubinaemia fell rapidly as he improved. Six cases of moderate to severe secondary anaemia are tabulated below as a contrast to those of pernicious anaemia; it will be seen that none of them gave a bilirubin value above normal.

TABLE VII A. *Secondary Anaemia.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
37	F	c. 11	0	0.5	(?+)	0	clin.	Severe aplastic anaemia. R.B.C. 1,000,000
38	M	62	0	<0.5	0	0	} P.M.	No cause for anaemia found.
		5 weeks later	0	0.5	0	0		Colour index always low
39	M	29	0	0.35	0	0	clin.	R. B. C. 1,250,000 R. B. C. 3,470,000. Chlorotic type. ? Cause
40	F	67	0	0.5	(?+)	0	clin.	Low colour index. R. B. C. 3,000,000
41	F	29	0	0.5	0	0	clin.	R. B. C. 3,630,000.
42	M	52	0	0.4	0	0	clin.	Rectal polypi ? New growth of stomach. R. B. C. 1,450,000

*Icterus neonatorum.* This condition may be considered under the head of haemolytic jaundice. An investigation was made of blood obtained by squeezing the umbilical cords of infants immediately after delivery. The results in thirty-eight cases show that there is almost invariably a latent jaundice present at birth. In twenty-four cases between 1.1 and 2 units of bilirubin were present in the blood, the average being 1.4 units. In five cases 2 or more units were present, the greatest amount being 3 units; in seven cases between 0.6 and 1 unit was found. Only two cases gave values below that of a normal adult, one of 0.4 and one of 0.2 unit. In about half the cases haemolysis had occurred in the serum, and it could not be certainly determined whether the reaction was direct or indirect (haemoglobin interferes with the direct reaction but is precipitated in performing the indirect test). Whenever the nature of the reaction could be determined the direct test was negative.

Van den Bergh's test thus suggested that icterus neonatorum is not obstructive in origin, and that it is partly due to factors which come into



play before birth. These results may help to elucidate the vexed question of the aetiology of icterus neonatorum, into which it is not proposed to enter here. It is of interest, however, to consider the relation between the amount of bilirubin in the serum at birth and the occurrence of jaundice subsequently. As the table shows, there is only a rough correspondence. While cases with a high bilirubinaemia at birth commonly developed jaundice later, and cases with low bilirubin in their blood usually failed to do so, yet it was impossible to foretell with certainty from the amount of the pigment in the umbilical vein whether jaundice would appear or not. Hirsch (7) and Ylppö (15) have shown that the bilirubin content of the serum rises to a variable height for the first few days of life and then rapidly falls. It is the height reached after a few days which determines the appearance of clinical jaundice; the height of the starting-point, as it were, is thus apparently one factor only in deciding whether a child shall be jaundiced or not.

TABLE VIII. *Icterus Neonatorum.*

	Number of Cases with subsequent Jaundice.	Number of Cases without subsequent Jaundice.	Percentage with Jaundice.
Bilirubinuria at birth under 0.5 units	0	2	0
Bilirubin 0.5 to 1	1	6	14
" 1.1 to 1.5	2	8	20
" 1.6 to 2	7	7	50
" 2.1 to 2.5	2	1	67
" 2.6 to 3	2	0	100

Different writers vary greatly in their statements as to the incidence of jaundice in the new-born. Nothing has been counted as clinical jaundice in the table above which was not very definitely such, the icteric hue being deeper than the colour of the average infant of two or three days old. It may be mentioned that two infants, a few weeks premature, showed 1.1 and 1.3 units respectively.

*C. Cases of jaundice not frankly obstructive or frankly haemolytic.*

TABLE IX. *Catarrhal Jaundice.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
43	M	58	18	+	++	+	clin.	
44	F	52	20	19	++	+	clin.	
45	M	48	6	6	++	+	clin.	
46	F	34	20	16	++	+	clin.	
47	M	29	?+	6.25	++	+	} clin.	Or ? cholelithiasis. Haemolysis in serum on first occasion and direct test doubtful
11 days later			4.7	1.1	+	+		
48	F	34	4.4 (biphasic)	0.75	++	0	clin.	
49	F	28	2	1.3	+	0	op.	Nothing abnormal at operation
50	F	42	10	+	++	+	clin.	
51	F	9	10	+	++	+	} clin.	Laevulose tolerance test showed considerable damage
"	"	"	4	1.2	+	0		
52	F	22	13.3	+	++	+	clin.	

This group includes cases of jaundice presumably due to liver-cell damage or to a combination of factors. In some instances, notably those of catarrhal jaundice and cirrhosis of the liver, the exact causation of the jaundice is still obscure.

TABLE X. *Toxic Jaundice.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
53	F	53	22	19	++	No note	P.M.	Fine cirrhosis. Much necrosis. ? Secondary to toxic hepatitis
54	M	22	21 (biphasic)	+	++	+	} clin.	4 silver-salvarsan injections 3 mos. before. Laevulose test showed liver damage
"	"	"	6-5 (biphasic)	4	++	+		
55	F	23	3-4	+	+	0	clin.	Probably $\text{CHCl}_3$ poisoning. Forcibly delivered 6 days before
56	F	5	? 0	0-9	0	0	P.M.	Delayed chloroform poisoning

It will be seen (Table IX) that all the cases of catarrhal jaundice showed a direct reaction. Other workers (1, 11, 14) have usually found a direct reaction in catarrhal jaundice, though an indirect reaction alone has also been met with not uncommonly, especially with low bilirubin values and with fading jaundice (1, 4, 11). As mentioned above, this occurs also in cholelithiasis. Schiff and Eliasberg (12), on the other hand, record a series of cases in children in which an indirect reaction persisted throughout the course of the disease. Their work will be commented upon later.

There is an increasing trend of opinion nowadays to the view (2, 9), based on the clinical character of the disease, on histological evidence, and on work with liver-function tests, that catarrhal jaundice is in most cases a hepatitis and not primarily a cholangitis. Liver-cell damage is usually assumed to lead to an indirect van den Bergh's reaction in the serum (9), and van den Bergh's test thus seems at first to controvert the modern conception of catarrhal jaundice. McNee (10) and others seem to assume that there must be an obstruction to the fine capillaries as well as a hepatitis to account for the direct reaction. Histological observations by Eppinger (3) do not substantiate this, though it is true that we have no record of what van den Bergh's test might have revealed in the cases he studied. It is quite conceivable that the jaundice due to liver-cell damage may be associated with either a direct or an indirect reaction in the serum. It will be noted that Cases 51 and 54 showed evidence of liver-cell damage on performing the laevulose tolerance test.

Cases of cirrhosis of the liver yielded either a normal result as regards bilirubinaemia; or, in the presence of obvious jaundice, a direct reaction; or, occasionally, when there was latent jaundice, an indirect reaction.

TABLE XI. *Cirrhosis of the Liver.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
57	F	38	+	3	+	0	clin.	Syphilitic; ascites.
58	F	50	0	0.5	0	0	clin.	Splenomegaly
59	M	50	0	0.5	0	0	op.	Ascites
60	M	58	3.5	3.5	+	+	clin.	Ascites
14 days later			+	1.5	+	?		
61	F	26	2.5	1.75	?+	0	P.M.	Ascites. Severe anaemia. Nosplenomegaly
3 months later			4	4	+	0		
			(biphasic)					
62	M	17	0	0.6	0	0	clin.	Ascites
63	M	54	0	1.3	0	0	P.M.	Also malignant endocarditis
11 days later			0	1.3	0	0		
64	F	8	20	18.5	+	No record	P.M.	Probably congenital syphilis.
								Died in coma
65	M	50	11.6	8.2	+	+	P.M.	Died in coma. Had also malignant endocarditis
A few days later			6.7	6.2	+	+		
66	F	57	0	0.5	0	0	P.M.	Haemochromatosis
4 days later			0	0.5	0	0		
67	M	9	+	1.5	0	0	clin.	
68	M	60	0	0.5	0	0	P.M.	Patient had also arterio-sclerotic kidneys
69	F	55	0	0.5	0	0	P.M.	

TABLE XII. *Morbus Cordis.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
70	F	10	+	2.25	0	0	P.M.	Large liver. Note lower bilirubin-aemia at time of death than earlier
7 months later			0	0.5	0	0		
71	F	50	0	0.5	0	0	P.M.	Also nephritis
72	M	60	0	2	0	0	clin.	Gross failure
73	M	36	0	7.5	+	? 0	clin.	
4 days later			0	1.5	?	? 0		
74	M	20	4	3.75	0	? 0	clin.	Bilirubinuria earlier
			(biphasic)					
75	F	30	0	0.75	0	0	clin.	Large liver
76	F	22	0	0.3	0	0	P.M.	Malignant endocarditis. No gross failure
77	F	48	0	2.3	?+	0	clin.	Large liver
78	F	49	0	0.5	0	0	clin.	Large liver
79	M	41	+	1.3	0	0	P.M.	No histological evidence of obstruction in liver
			(biphasic)					
80	F	?	? 0	<0.5	0	0	clin.	Malignant endocarditis. No gross failure
81	M	57	0	0.4	0	0	P.M.	Large liver
82	F	36	? 0	0.5	0	0	clin.	? Malignant endocarditis. No gross failure
83	F	52	0	1.6	0	0	clin.	Hyperpiesia. Gross failure

*Cases of heart disease* without gross heart-failure all gave a normal result. Cases with gross failure, and especially with enlarged livers, usually had latent, if not obvious jaundice, sometimes with an indirect, sometimes with a direct or biphasic reaction. Hepatic enlargement and hyperbilirubinaemia did not, however, always go hand in hand. Fishberg (5), in America, has especially studied van den Bergh's test in heart disease; his conclusions are similar to the above. It is rare that one has the opportunity of histological examination of livers in which liver-cell damage is likely to be an uncomplicated factor. The fact that Case 79 gave a biphasic reaction and yet showed no histological evidence of obstruction to large or small bile-ducts is important in this connexion.

TABLE XIII. *General Infections.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
84	M	30	0	1	+	0	clin.	General pneumococcal infection
85	M	32	2	2.1	+	+	}	clin. Lobar pneumonia
		5 days later	< 0.8 (biphasic)	0.5	0	0		
86	M	44	?	1.0	0	0	P.M.	Paratyphoid B. Colitis
87	F	27	0	1.3	0	0	}	P.M. Typhoid
		A few days later	0	0.5	0	0		
88	M	22	?	0.6	0	0	}	clin. Paratyphoid B
		2 days later	0.6 (biphasic)	0.6	0	0		
		12 days later	0	0.5	0	0		
89	M	29	0	0.4	0	0	clin.	Paratyphoid C. 2 yrs. ago. Thromboses since. Polycythaemia
90	M	1½	0	0.8	0	0	P.M.	Meningococcal meningitis. (See also Case 22)
91	M	30	0	< 0.5	0	0	clin.	Purpura. ? Septicaemia
92	F	65	0	0.5	0	0	clin.	Infection with myelocytic reaction. ? Leukaemia
93	M	10	0	0.5	0	0	clin.	Bronchitis. Splenomegaly

TABLE XIV. *Local Infections of Liver.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
94	M	34	0	0.8	0	0	clin.	Amoebic hepatitis
95	M	31	0	< 0.5	0	0	clin.	? Amoebic hepatitis
96	M	42	0	0.75	0	0	P.M.	Streptococcal abscess of liver. Hepatic vein thrombosis

TABLE XV. *Lymphadenoma.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Biliru- binuria.	Basis of Diagnosis.	Comments.
97	M	50	2	2.6	+	0	P.M.	Gross changes in liver

TABLE XVI. *Splenic Anaemia.*

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Biliru- binuria.	Basis of Diagnosis.	Comments.
98	F	32	0	1.6	0	0	op.	Blood from basilic vein at op. Blood from splenic vein at op.
		3 weeks later	? 0	1	0	0		
		4½ months later	1.2	(about) 1.1	+	0		
		5 months later	+	1.5	+	No notes		
			(biphasic) 3	2				
"	"	"	(biphasic)					
99	F	54	? 0	0.9	+	0	clin.	9 yrs. after splenectomy
100	M	38	0	0.5	0	0	op.	

The above cases of infections and other conditions, in which liver damage probably played a part, showed at times a normal result, sometimes a direct reaction, sometimes an abnormally high indirect reaction. Bilirubinaemia high enough to cause clinical jaundice was usually associated with a direct reaction. Case 98 is of interest, an indirect reaction being seen at first, and a direct reaction later. In this case, through the kindness of Mr. Sherren, I was able to compare the bilirubin content of the peripheral blood with that of splenic vein-blood obtained at the time of operation for splenectomy. There was definitely more bilirubin in the splenic blood, thus confirming some observations by van den Bergh (14) and others, and suggesting that the spleen may be a site of origin of bilirubin. This is unfortunately the only observation on this point that I was able to make.

D. *Control cases.* It now remains to tabulate cases in which the individual was either normal or suffering from a disease unlikely to involve the liver or the bile-pigment metabolism.

Two diabetic cases, 110 and 111, gave a normal van den Bergh's reaction, though the skin had a marked yellowish tinge, probably from carotin.

To these must be added twenty-five observations on sixteen patients with nephritis. It will suffice to say that in these nephritic cases bilirubinaemia was of normal or less than normal amount; usually, too little pigment was present for accurate measurement. Cases of almost all types of nephritis were studied. There was one exceptional instance, that of a man of 53, whose serum gave an indirect reaction with 2 units of bilirubin. His conjunctivae were yellowish on admission; he died a month later of uraemia. Gall-stones were found *post mortem* in his gall-bladder, but no signs of past or present obstruction in his biliary passages. Although the colour-reaction due to bilirubin was usually

less than normal, another unexplained colour-reaction was encountered in eight of these cases of nephritis, all of which were severe cases of uraemia with over 220 mgm. of urea per 100 c.c. of blood. This consisted of an orange-buff colour which gradually developed after performing the indirect test and which gave a transient cherry-pink if caustic soda was added some hours later. The cases are tabulated and the reaction discussed in a separate paper (16).

TABLE XVII.

No.	Sex.	Age.	Dir. Test.	Ind. Test.	Jaund.	Bilirubinuria.	Basis of Diagnosis.	Comments.
101	M	26	0	0.5	0	0	clin.	Normal
102	M	c. 23	0	0.5	0	0	clin.	Normal
103	F	22	0	0.6	0	0	clin.	Constipation
104	M	15	0	0.5	0	0	op.	3 wks. after splenectomy for trauma
105	M	49	0	0.5	0	0	clin.	? Renal colic
106	M	26	0	0.5	0	0	clin.	? Renal colic
107	F	22	0	0.5	0	0	clin.	Syphilitic meningitis. Recent course of '914'
108	F	?	0	0.5	0	0	clin.	Cerebral syphilis. Recent course of '914'
109	M	50	0	0.3	0	0	clin.	Tabes dorsalis. Recent course of sulpharsenol
110	M	21	0	0.5	0	0	clin.	Diabetes. Xanthoma
111	M	53	0	0.5	0	0	clin.	Diabetes. Yellowish
112	M	30	? 0	0.5	0	0	clin.	Diabetes. Coma
113	F	27	0	< 0.5	0	0	P.M.	Ulcerative colitis
114	M	38	0	< 0.5	0	0	clin.	Colitis
		4 weeks later	0	< 0.5	0	0		
115	F	14	0	0.5	0	0	clin.	Ulcerative colitis
		10 days later	0	0.5	0	0		
116	M	20	0	0.5	0	0	clin.	? Sarcoma of back
117	F	42	0	0.5	0	0	clin.	Syphilis. Polycythæmia; splenomegaly
118	M	26	0	0.5	0	0	P.M.	Pulmonary and glandular tuberculosis

*E. Van den Bergh's test in pathological fluids.* Haematoidin, which is isomeric with bilirubin and usually considered identical with it, is known to be formed locally from haemoglobin in pathological fluids. Van den Bergh applied his test to determining whether the blood in a given haemorrhagic fluid had been present for some time or was introduced at the time of puncture. In the former case a considerable amount of bilirubin, giving, of course, only the indirect reaction, might be expected to be present; in the latter case there would be none or, at most, no more than in the blood-serum. I was able to confirm these results in a small number of cases.

*Cerebro-spinal fluids.* Normal fluids yield no colour at all with the diazo-reagent. One case of cerebral haemorrhage with a yellow tinge to the supernatant fluid had 0.25 unit of bilirubin in the cerebrospinal fluid. A yellowish fluid



obtained from two cases of tuberculous meningitis gave no colour reaction. Perhaps the yellow colour was due to a lipochrome. One case of lymphadenoma (No. 97) had a yellow cerebro-spinal fluid containing 0.7 unit of bilirubin, the reaction being direct. The serum of this patient contained 2.6 units (direct reaction), and it was not beyond possibility that the yellow colour in the fluid was due to a slight accidental admixture of serum when the fluid was obtained at the autopsy. Two other cases with definite jaundice showed no bilirubin in the cerebro-spinal fluid. It may be argued that the clinical value of this test as pointing to a haemorrhage of one or two days' standing is little: naked-eye inspection of the supernatant fluid after centrifugalizing would show as much. The possibility of error from the occasional presence of lipochrome in the cerebro-spinal fluid must, however, be borne in mind.

*Pleural effusions.* One case of haemorrhagic effusion following pneumonia showed 1.8 units of bilirubin; another, due to new growth, contained 6.8 units, the reaction being indirect in both cases. A third case, in which there was definite clinical evidence that the blood was introduced at the time of puncture, contained less than 0.3 unit.

*Ascites.* One case with haemorrhagic ascites due to new growth contained 3.7 units of bilirubin in the fluid. One case of lymphoid leukaemia with a history of old bleeding into a peritoneal exudate showed only half a unit. All the other cases examined had more or less jaundice, and all showed considerably less bilirubin in their ascitic fluids than in their blood.

TABLE XVIII. *Ascitic Fluids.*

No. of Patient. (See Previous Tables.)	Diagnosis.	Test in Serum.	Test in Fluid.
61	Cirrhosis hepatis	Biphasic 4 units	Indirect 1 unit
57	"	Direct c. 3 "	Direct 0.5 "
63	" and endocarditis	Indirect 1.3 "	Indirect = trace
65	"	Direct 6.7 "	Direct 2 units
70	Cardiac failure	Biphasic 0.5 "	Indirect 0.5 "
20	New growth of liver	Direct 13 "	Biphasic 1.6 "

*Other fluids.* A lump in the back of a youth of 20 (No. 116) was aspirated and pure blood obtained. This contained 4.5 units of bilirubin (indirect). Blood from his basilic vein was normal in its bilirubin content. This suggested that a haematoma had been aspirated—a fact later confirmed by operation, when a haematoma in connexion with a malignant growth was found.

*Conclusions from the Results: the Clinical Value of van den Bergh's Test.*

A. As a quantitative test for bilirubin in the serum. The test is undoubtedly of value in this respect. It enables us to detect 'latent jaundice' and to estimate it quantitatively. Previously bile-pigment retention could be recognized only when it had reached a fairly high degree: the more sensitive test now available will be of value in drawing attention to involvement of the

liver in a disease process. As a test of liver function it is admittedly crude, since it may give a normal result when other tests show evidence of damage or when the liver is known to be diseased; but it has one great advantage in that it is very simple to perform. It enables us to detect the presence of a haemolytic process in the body and thus to distinguish a pernicious from a cancerous or other secondary anaemia. It enables us to follow the course of a jaundice in regard to whether it is increasing or decreasing. Skin pigmentation is a much poorer index, for it alters slowly as compared with the bilirubinaemia. Van den Bergh believes that the test may be of use in pointing to a failure of the heart-muscle in cases of nephritis or of oedema of obscure origin, or in cases of pulmonary emphysema. I have not met with cases in which it was of value in this direction, but quite probably there are such. The test will also enable one to decide whether a yellow pigmentation of the skin or serum is really due to the presence of bilirubin.

B. *As a quantitative test for bilirubin in pathological fluids.* Here, as described above, van den Bergh's test has a considerable value in helping us to decide if a haemorrhagic effusion or cerebro-spinal fluid was previously blood-stained or if the blood entered it at the time of puncture, and whether blood which has been aspirated comes from a haematoma or not.

C. *As a means of distinguishing between different types of jaundice.* All cases of frank obstructive jaundice, except at the immediate onset or at the end, give a direct reaction. All cases of haemolytic jaundice give an indirect reaction. Cases of jaundice due to liver-cell damage may give a direct or indirect reaction—often a mixture, a biphasic reaction. Since it is almost wholly the last group which gives rise to clinical difficulty, the test is not often helpful here: an obstructive jaundice is rarely hard to tell from a haemolytic one by its clinical features. Thus, while the distinction between the direct and indirect reactions is one of great theoretical interest, it appears to be of little aid in the discrimination of many doubtful cases. It is of no value in distinguishing catarrhal from obstructive jaundice.

The statement that damage to the liver-cells can by itself cause a direct reaction in the serum may not be universally accepted and is admittedly hard to prove. It is, however, suggested by the occurrence of a direct reaction in catarrhal jaundice, heart failure, and other conditions where in many cases histological evidence of obstruction is, to say the least, difficult to demonstrate. It is easily explicable on theoretical grounds. Let us for the moment accept the tempting but unproven hypothesis that bilirubin giving the indirect reaction is formed outside the liver-cells, is excreted by them, and converted in the process into a form giving a direct action. Parenchymal damage of such sort that bilirubin cannot be passed on by the liver-cells will cause retention in the blood-stream of bilirubin giving an indirect reaction. But another process may be at work. Eppinger (3) argues that parenchymal damage may cause jaundice by destruction of liver-cells here and there, leaving a way for bile excreted by the surviving elements to escape from the bile capillaries back into the lymph

and blood spaces. A direct reaction might be expected with jaundice caused in this way. Granting so much, it might be supposed that a mild degree of liver-cell damage would cause bilirubinaemia giving an indirect reaction; while severer grades of damage would give rise to a direct reaction; nor would there be any necessity for invoking an obstructive catarrh of the bile capillaries.

*The Excretion of Bilirubin through the Kidneys.*

It is well known that in purely haemolytic jaundice bilirubinuria does not usually occur. In other forms of icterus it commonly does occur if the jaundice is deep enough. Van den Bergh was able to throw light on the conditions governing the excretion of bilirubin in the urine, and to formulate the following rule: In morbid conditions in which the serum gives only the indirect reaction, bilirubinuria never occurs. When the serum gives a direct reaction, bilirubinuria occurs as soon as the bilirubin in the blood reaches about 4 units. In other words, the kidneys are impermeable to the bilirubin which gives the indirect reaction, and permeable to that giving the direct one when the concentration reaches a threshold value of 4 units. McNee (10) and Lepehne (8) have confirmed these results. So have almost all other workers. Retzlaff (11), however, gives tables of his results in many cases of jaundice, and though he himself apparently paid no attention to the matter of a renal threshold for bilirubin, he cites five cases with blood bilirubin (direct) of over 4 units (one case of 9.3 units) *without* bilirubinuria and one case *with* bilirubinuria and only 2.5 units in the serum. Schiff and Eliasberg (12), on the other hand, do not believe that a direct or indirect reaction has anything to do with the passage of bilirubin into the urine. They quote a series of cases of catarrhal jaundice and one of congenital atresia of the bile-ducts in which the blood-serum gave only an indirect reaction, although there was a plentiful bilirubinuria. These results are so wholly opposed to those of other workers that one must be reluctant to accept them until they are confirmed. Mention must further be made of the work of Haessler, Rous, and Broun (6), who mention the occurrence of bilirubin-stained cells and bilirubin crystals in the urine in various conditions including icterus neonatorum, in which only an indirect reaction occurs.

If there are two forms of bilirubin circulating in the blood, one of which can pass through the kidneys (direct form) and the other not (indirect form), it is rather surprising that van den Bergh and others should have found such a constant threshold value for bilirubin irrespective of its form; for one may recall that our methods of estimation give the sum of 'direct' and 'indirect' forms. It would be expected that cases showing a biphasic reaction might have bilirubinaemia of over 4 units and yet no bilirubinuria, since the 'direct' kidney-permeable constituent of the bilirubin might lie below 4 units. I have made a number of observations bearing on this point. Their general tendency is to show that the threshold value of the kidney is not quite constant,

but that it lies near 4 units: with the standard I used it was usually around 3.5 units.

No patient whose serum gave only an indirect reaction excreted any bile in the urine. It is true that only four such cases were met with having more than 4 units of indirect bilirubin in the blood: these were No. 23 (acholuric jaundice) with 8.5 units, No. 28 (pernicious anaemia) with 5 units, No. 30 (pernicious anaemia) with 5 units, and No. 73 (jaundice from cardiac failure) 7.5 units. But all the cases giving a direct reaction of over 4.4 units showed a bilirubinuria and, with a single exception, no case giving a direct reaction of under 3.5 units showed bilirubinuria. The cases with values near the threshold are tabulated below. For further details of the cases the previous tables can be referred to. The test for bilirubinuria employed was either Gmelin's or that of oxidation with iodine.

TABLE XIX. *The Bilirubin Threshold.*

No.	Disease.	Direct Reaction.	Indirect Reaction.	Bilirubinuria.
Male, aged 54	? Gall-stones	4.8	+	+
	? New growth			
6 days later	" "	3.5	+	+
16 days later	" "	4	+	+
9	Carcinoma of common duct	4 (biphasic)	4	+
48	Catarrhal jaundice	4.4 (biphasic)	0.75	0
51	" "	4	1.2	0
55	Chloroform poisoning	3.4	+	0
60	Cirrhosis	3.5	3.5	+
61	"	4 (biphasic)	4	0
74	Cardiac failure	4 (biphasic)	3.75	0
85	Pneumonia with jaundice	2	2.1	+
5 days later	" " "	0.8 (biphasic)	0.5	0

It will be seen that two cases had bilirubinuria when there were only 3.5 units of bilirubin in the serum. Three cases with 4 units or just over and no bilirubinuria gave biphasic reactions, which would suggest that the direct constituent of their bilirubin might have less than the threshold value. But in the main van den Bergh's findings are confirmed, the difference in the figures being but slight. Case 85, however, affords a striking exception. Here bilirubinuria occurred with a serum-value of only 2 units, indicating a well-marked variation in the kidney threshold for bilirubin. This patient had bile in his urine immediately after, as well as before his blood was withdrawn for examination.

#### *Summary.*

1. Van den Bergh's test has a considerable clinical value as a method of quantitative estimation of bilirubin in the blood. It enables one to follow the progress of jaundice quantitatively and to detect it when latent. With its aid one may distinguish a pernicious from a secondary anaemia.

2. Frankly haemolytic can be distinguished from frankly obstructive jaundice by means of the test, but as a means of differentiating icterus due to liver-cell damage from other types of jaundice the value of the method is slight. Theoretical reasons are put forward why liver-cell damage should be able to cause either the direct or indirect diazo-reaction.

3. There is a kidney-threshold for direct bilirubin corresponding to 3.5 or 4 units of bilirubin in the blood. Some slight individual variation occurs.

## REFERENCES.

1. Brulé, Garban, and Weissmann, *Presse méd.*, Paris, 1922, xxx. 2. 986.
2. Brulé, *Recherches sur les Ictères*, Paris, 3rd edit., 1922.
3. Eppinger, H., *Verhandl. der deutsch. Gesells. f. Inn. Med.*, München, 1922, xxxiv. Kongr. 15.
4. Feigl, J., and Querner, E., *Zeitsch. f. d. ges. exper. Med.*, Berlin, 1919, ix. 153.
5. Fishberg, A. M., *Journ. Amer. Med. Assoc.*, Chicago, 1923, lxxx. 1516.
6. Haessler, H., Rous, P., and Broun, G. O., *Journ. Exper. Med.*, New York, 1922, xxxv. 533.
7. Hirsch, A., *Zeitsch. f. Kinderh.*, Berlin, 1913, Orig. ix. 196.
8. Lepehne, G., *Deutsch. Archiv f. klin. Med.*, 1920, cxxxii. 96.
9. McNee, J. W., *Brit. Med. Journ.*, 1922, i. 716.
10. McNee, J. W., *Quart. Journ. Med.*, Oxford, 1922-23, xvi. 390.
11. Retzlaff, K., *Zeitsch. f. d. ges. exper. Med.*, Berlin, 1923, xxxiv. 133.
12. Schiff, E., and Eliasberg, H., *Klin. Woch.*, Berlin, 1922, ii. 1891.
13. van den Bergh, A. A. Hymans, and Snapper, *Deutsch. Arch. f. klin. Med.*, 1913, cx. 540.
14. van den Bergh, A. A. Hymans, *Der Gallenfarbstoff im Blute*, Leiden, 1918.
15. Ylppö, A., *Zeitsch. f. Kinderh.*, Berlin, 1913, Orig. ix. 208.
16. Andrewes, C. H., *Lancet*, Lond., 1924, i. 590.

## THE RELATION BETWEEN THE BASAL METABOLIC RATE AND THE PULSE-PRESSURE IN CONDITIONS OF DISTURBED THYROID FUNCTION

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### I

#### *General Considerations.*

DURING recent years the study of disturbances of thyroid function has been considerably advanced by estimations of the basal metabolic rate. The findings for this rate have been shown by numerous observers to give a very satisfactory indication of clinical severity and progress. Owing to the fact, however, that accurate determinations of the basal metabolic rate require time, a certain amount of skill, and somewhat elaborate apparatus, it would manifestly be an advantage if similar definite information could be obtained by some more simple means. Moreover, although as a general rule the findings for the basal metabolic rate when determined by a competent observer are very accurate, yet occasionally there may be some gross error, possibly due to a leak in the apparatus or some error of technique or of calculation. Hence it seems to be of importance that there should be some simple means whereby the findings for the basal metabolic rate might be controlled.

Read (1) has recently shown that the pulse-rate and pulse-pressure in cases of hyperthyroidism vary in the same direction as the basal metabolic rate, and that a combination of these two factors gives a better measure of the circulatory response to variations of metabolism than either one alone. From an analysis of 300 observations this author has evolved a simple formula for predicting the basal metabolic rate from the pulse-rate and pulse-pressure. The formula is

$$\text{B.M.R.} = 0.683 (\text{P.R.} + 0.9 \text{ P.P.}) - 71.5.$$

This formula gives the basal metabolic rate to within  $\pm 10$  per cent. in 60 per cent. of cases and to within  $\pm 20$  per cent. in 91 per cent. of instances. The author states, however, that accuracy of prediction is difficult to obtain because of individual variations of pulse-rate and pulse-pressure.

(Q. J. M., Oct., 1924.)



Stewart (2) has shown that in a case of Graves's disease the local blood-flow in the hands is greatly increased. Theoretically an increase of metabolism beyond a certain point would demand an increase of blood-flow, although, as Douglas and Haldane (3) have shown, this increase is not a simple linear function of the increase of metabolism. This is doubtless due to the fact that the carrying power of the blood for oxygen and carbon dioxide is in excess of the usual resting needs of the normal individual. An increased blood-flow may be shown by an increase in pulse-rate, although this is not necessarily the case, for it has been shown by Meakins, Dautrebande, and Fetter (4), and by Barcroft, Bock, and Roughton (5), that an increase in pulse-rate may be associated with marked diminution in minute volume of blood-flow in certain conditions of cardiac abnormality and failure. Moreover in certain individuals the reverse may be the case, namely, that an increased systolic output may result in an increased minute volume of blood-flow without any rise of pulse-rate. Indeed Barcroft (6) and his associates have shown that in certain circumstances there may be an increased minute volume of blood-flow associated with a diminished pulse-rate. Hence we can see that an increased pulse-rate may not indicate quantitatively an increased metabolic rate even in normal individuals, probably far less so under pathological conditions. Sturgis and Tompkins (7) have investigated the relations between pulse-rate and basal metabolic rate in cases of hyperthyroidism. Their conclusions are based upon 496 observations on 154 patients. The individual variations were considerable. Thus one patient may have a pulse-rate of 90 with a basal metabolic rate as high as +79 per cent., while another may have a pulse-rate of 108 with a metabolism of +12 per cent. These, however, are extremes, and when one considers the averages it must be conceded that increases of pulse-rate follow very closely the increases of basal metabolic rate. Moreover in any given case the variations of basal metabolic rate follow as a rule very closely the variations of pulse-rate, especially if the latter be expressed as percentage increase or decrease from an assumed normal.

Another possible guide to prolonged disturbances of basal metabolic rate might be changes of body-weight. Yet these, to be of exact quantitative significance, would have to be estimated under strictly standardized conditions both as regards diet and bodily activity.

Changes in the basal metabolic rate differ from changes in body-weight and pulse-rate in that they necessarily take into consideration differences in size, age, and sex of the individuals, so that by taking the basal metabolic rate expressed as a percentage change from the average normal we have a figure which is a definite index and which is not appreciably affected by individual peculiarities. In other words, we have a fact of fundamental biological significance expressed in terms so general as to enable us to compare any one case with any other case both as regards severity and progress. It is possible, however, that pulse-rate, if expressed as a percentage change from the average normal for an individual of the same size, age, and sex, might be of the same fundamental significance.

In spite of the fact that the relation between blood-flow and metabolism

may not always be a simple linear function, it seems probable that anything which might give an approximate indication of an altered rate of blood-flow would also give some indication of a change in metabolism. A low diastolic blood-pressure together with a normal or increased systolic blood-pressure must as a rule indicate that the blood is flowing more freely through the periphery. Therefore, unless there be aortic regurgitation or arterio-venous aneurysm, an increased pulse-pressure might afford a valuable clinical indication of increased blood-flow and show a certain degree of correlation with increased metabolism, except possibly in conditions of anaemia where owing to diminished blood viscosity the peripheral resistance is lowered. So far as we are aware there are no extensive studies of pulse-pressure in cases of anaemia recorded in the literature. Boothby (8) considers 'An increased pulse-pressure in the absence of hypertension and associated with an increased pulse-rate without many exceptions indicates an increased circulation rate which in turn signifies an elevated basal metabolic rate'. Beall (9) considers that a pulse-pressure of more than 50 mm. favours the presence of hyperthyroidism, while a pulse-pressure below 50 mm., if hypertension is excluded, favours the absence of hyperthyroidism. Harris (10) points out the unusual factor of an increased pulse-pressure together with an increased pulse-rate. So far as he is aware this occurs only in hyperthyroidism. In the course of numerous clinical observations one of us (J. E.) was impressed by finding that in cases of hyperthyroidism the pulse-pressure was constantly greater than normal, and the increase of pulse-pressure seemed roughly proportional to the severity of the symptoms. Moreover the increase of pulse-pressure was usually brought about by a lowering of the diastolic pressure. The systolic pressure showed considerable variations in different cases, but on the average showed a moderate increase above normal. At the time these observations were made the work of Read had not appeared, and it seemed of importance to attempt to correlate changes of pulse-pressure with those of basal metabolic rate. For some time the routine estimations of the basal metabolic rate for the Edinburgh Royal Infirmary were carried out by one of us (H. W. D.), and this afforded a suitable opportunity for collecting the necessary data.

#### *Methods.*

The estimations of the basal metabolic rate were carried out by a modified Douglas bag method described in detail by Meakins and Davies (11). Immediately after taking the sample of expired air from the patient, the systolic and diastolic blood-pressures were determined by the auscultatory method. The apparatus used was of the Tycos type, the pneumatic cuff being 11.5 cm. in breadth. The correctness of the gauge reading was checked from time to time by comparison with a mercury manometer. The pulse-rate was taken several times during the ten-minute period of collection of expired air, and the mean of these several observations recorded. We have figures for pulse-rate, metabolic rate, and

blood-pressure (systolic and diastolic), all taken under basal conditions in over 200 instances, and in a variety of clinical conditions. It is not our purpose to discuss the absolute value of blood-pressure readings. Whatever this may be our figures are of relative value in that the observations were always made by the same individual (H. W. D.), using the same instrument and as far as possible the same criteria for systolic and diastolic pressures. The diastolic pressure was taken as the point where the sounds over the brachial artery became just inaudible. This was necessary because in many of the cases under investigation it was impossible to observe any sharp point where the sounds became muffled. We recognize that this criterion may not give the exact diastolic pressure, yet for comparative purposes the error is as a rule quite small, especially when compared with the magnitude of the pulse-pressure. As is usual in estimating the basal metabolic rate, the height and weight (the latter corrected for the weight of clothes worn) were always determined for each observation. In some instances we have one or two observations only on a given individual, but in other cases we have been fortunate in being able to make a series of observations over a fairly considerable period. In the latter we give a short synopsis of the clinical notes, for the use of which we are indebted to Professor Meakins and Sir Harold Stiles.

*The General Correlation between Pulse-pressure and Basal Metabolic Rate.*

In Fig. 1 the values for pulse-pressure are plotted against those for the basal metabolic rate in 150 observations. Some of these represent single observations on single cases, while others are different observations, each at a different stage of the disease in certain cases. Some of these latter cases will be dealt with more fully in a subsequent section. All the cases where the basal metabolic rate was high were individuals suffering from hyperthyroidism, while those with low basal metabolic rate were cases of hypothyroidism. Those within the range of normality (approximately from  $-20$  to  $+20$  per cent. B.M.R.) were in a few instances normal students; others were cases of hyper- or hypo-thyroidism which had returned to normal; while the remainder were cases where the basal metabolic rate was estimated for diagnostic purposes and proved to be normal. It is at once apparent that in spite of considerable individual variation or 'scatter' there is a fair degree of correlation. Thus there are no cases with high basal metabolic rate where the pulse-pressure is not considerably above normal. Conversely there are few cases with normal or low basal metabolic rate where the pulse-pressure is not moderately low. As regards the latter some of the observations in the figure which appear to be moderately high are on cases shortly after operation, and in which the figures for pulse-pressure subsequently reached a much lower or more normal value. The two observations marked *b, b*, fall under this category. Yet it remains to account further for the considerable individual variation. At the time when each observation was made this variation was less apparent, and certain factors which might have been of importance were unfortunately neglected. The following ideas suggest themselves, however, and

we would advise consideration of them in future work. Firstly, the question of blood viscosity. It is obvious that the low diastolic pressure and consequent high pulse-pressure in these cases of hyperthyroidism depends in large measure, if not entirely, upon a diminished peripheral resistance brought about probably by a fairly general vaso-dilatation. Diminished blood viscosity would have a similar effect unless neutralized by vaso-constriction. Now anaemia, even of very moderate degree, would produce a considerable diminution of blood viscosity. Moreover, the increased general circulation rate which probably forms the most efficient means of compensating a moderate degree of anaemia would be associated with a certain amount of vaso-dilatation, at any rate in organs essential to normal existence. Hence in conditions of anaemia one would expect an increase of pulse-pressure without any corresponding increase of metabolism, while even moderate variations in blood viscosity and red-cell count would account for some of the 'scatter' in Fig. 1. Secondly, the various conditions of cardiovascular upset which frequently occur in cases of hyperthyroidism might so modify the conditions in the vascular system as to cause variations in whatever relation may exist between basal metabolic rate and pulse-pressure. Thus in cases of toxic adenoma of the thyroid where the systolic pressure is usually high there may be various degrees of circulatory failure, and it is hardly to be expected that this relation would be the same as in hyperplastic goitre or true Graves's disease where the patients are usually much younger and the affection much less chronic and associated with fewer signs of circulatory insufficiency. In Fig. 1 no distinction has been made between these two types of disturbed thyroid function. Thirdly, intercurrent sepsis or toxæmia would have a marked effect upon the vaso-motor system, causing possibly in some cases vaso-constriction and diminished pulse-pressure, in others further vaso-dilatation and increased pulse-pressure. The three observations marked *a, a, a*, in Fig. 1 are an example of this. They all relate to the case J. R., who in addition to exophthalmic goitre had septic tonsillitis, and subsequently a septic onychia which necessitated removal of a toe-nail. Fourthly, slight variations of temperature both of the patient and of the environment might have an appreciable and variable effect upon both the pulse-pressure and the basal metabolic rate. Lastly, the factor of error in the observations must be considered. In the case of the basal metabolic rate this would be not more than  $\pm 5$  per cent. The pulse-pressure is the difference between systolic and diastolic pressures, the possible error of the former being  $\pm 2$  mm. and the latter  $\pm 3$  mm., the total being  $\pm 5$  mm. Where the diastolic pressure is very low (high pulse-pressure) the error may be considerably greater. Thus with high pulse-pressures there may be an error of  $\pm 10$  m.m. or possibly more.

There is no reason for supposing that all the above factors are operative in only one direction, and one is justified in making a further analysis of the data of Fig. 1 by statistical methods. The results of Fig. 1 are shown in tabulated form in Table II (p. 60). Those observations which fall between two classes are shown as  $\frac{1}{2}$  in each, while those falling between four are shown as  $\frac{1}{4}$  in each.

Thus for a pulse-pressure of 20-30 mm. there are  $1\frac{1}{2}$  observations where the basal metabolic rate was - 40 to - 30 per cent., 2 where it was - 30 to - 20 per cent., and so on. Moreover one may average the basal metabolic rate for any given range of pulse-pressure. Thus for a pulse-pressure of 20-30 mm. we have  $1\frac{1}{2}$  observations where the average basal metabolic rate is - 35; 2 at - 25;  $2\frac{3}{4}$  at - 15; 1 at - 5; and  $1\frac{1}{2}$  at + 5. The average for all these is - 16.2 per cent. Similarly the vertical arrays give the range of pulse-pressure found in any given range of the basal metabolic rate, and the average pulse-pressure for each range of basal metabolic rate can be calculated. Thus we have 19 observations where the basal metabolic rate was - 10 to  $\pm$  0 and the average pulse-pressure is 46.8 mm. Table II shows clearly that as the basal metabolic rate increases the average pulse-pressure also increases, the slight irregularity in the basal metabolic

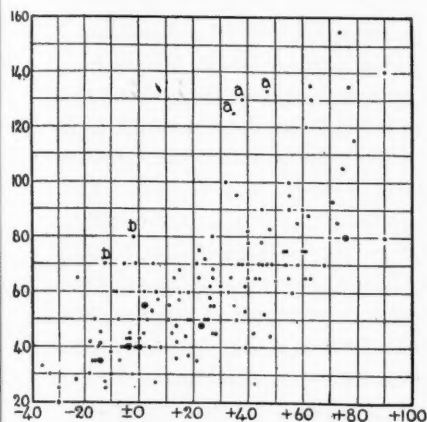


FIG. 1. Pulse-pressure and basal metabolic rate in 150 observations. Ordinates show pulse-pressure in mm. of mercury. Abscissae show percentage decrease or increase of basal metabolic rate. Points surrounded by circles represent two observations falling at identical points.

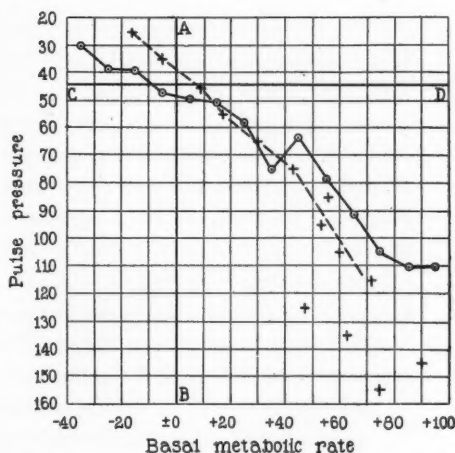


FIG. 2. + = mean basal metabolic rate plotted against pulse-pressure.  
○ = mean blood-pressure plotted against basal metabolic rate.  
Correlation diagram of pulse-pressure and basal metabolic rate.

rate range from + 30 to + 40 per cent. being due mainly to the three observations on the case of J. R. already referred to. Similarly the average basal metabolic rate shows a steady increase with increasing pulse-pressures. The irregularities occurring with the higher ranges of pulse-pressure may be accounted for by the fewness of the observations. It is clearly manifest, however, that in averaging a large number of observations there is a very close relationship between the basal metabolic rate and pulse-pressure. This close relationship can also be shown graphically (Fig. 2), the average basal metabolic rate for any given range of pulse-pressure being shown by crosses, and the average pulse-pressure for any given range of the basal metabolic rate by small circles. It is obvious that in the absence of all correlation between the two factors the averages of the basal metabolic rates for all ranges of pulse-pressure would be the same, and would



therefore fall along a vertical line, as for example *A, B*. In other words, whatever the pulse-pressure the average basal metabolic rate would approximate to a constant and presumably normal value. Conversely the average pulse-pressure would remain the same for all ranges of basal metabolic rate and would presumably lie along a horizontal line, as for example *C, D*. When the two lines representing the two sets of averages cut at an acute angle it indicates a close degree of correlation. Fig. 2 satisfies this latter condition, the deviation occurring in the classes with high basal metabolic rate and pulse-pressure being accountable for by the smallness of the number of observations.

#### *The Correlation in Individual Cases.*

In the preceding section we have pointed out that various complicating factors may disturb the relationship between pulse-pressure and basal metabolic rate. In certain cases it would be expected that some of these factors may remain more or less constant, while in some they may be absent altogether. The case of I. I. is an ideal one in this respect. The patient was a girl, aged 17, with a large parenchymatous goitre producing only slight pressure symptoms. On first admission her basal metabolic rate was on the lower limit of normality. This finding is not shown on the chart and tables, because at that time no observations of pulse-pressure were made. At this time there was no nervousness, tremor, tachycardia, nor any other signs of hyperthyroidism. She was discharged from hospital with prescriptions for cod-liver oil and for tincture of iodine. She reported eight and a half months later (March 1922) and was found to have a basal metabolic rate on the upper limit of normality and a pulse-rate of 80. At this time she was feeling very well, and the thyroid gland had slightly diminished in size. She was directed to continue the treatment and report again in a few weeks. She failed to return until the middle of July, when she was found to have all the symptoms of a moderate degree of hyperthyroidism. These promptly ceased after a few days' rest in bed and stoppage of the cod-liver oil and iodine. This case might almost be described as an experimental attack of hyperthyroidism induced by excessive iodine therapy in an otherwise healthy young individual. The findings for pulse-rate, pulse-pressure, and basal metabolic rate are shown graphically in Fig. 3. At first sight it would appear that the pulse-pressure findings exactly parallel those for the basal metabolic rate, but on plotting the other factors against the basal metabolic rate (Fig. 4) it is immediately apparent that this is not the case. It is to be regretted that the observations upon this case were not more numerous, yet from the existing data one is justified in saying that throughout the normal range of basal metabolic rate ( $-15$  per cent. to  $+15$  per cent.) the pulse-rate and pulse-pressure vary only slightly. From  $+15$  per cent. to  $+40$  per cent. there is a very sharp and rapid increase both of pulse-rate and pulse-pressure. Thereafter they tend to reach a maximum. Applying to these four results the formula of Read, the basal metabolic rates calculated



from the pulse-rates and pulse-pressures should be + 12 per cent., + 68.5 per cent., + 40 per cent., and + 2 per cent. Whereas actually they are + 14 per cent., + 55 per cent., + 22 per cent., and - 5 per cent. respectively. Read made the assumption that the relation between basal metabolic rate and the other two factors is a simple linear one, whereas Fig. 4 shows that this is not so in the case under consideration. If the pulse-rates and pulse-pressures be plotted against the *calculated* basal metabolic rates in this case, the curve approximates to a straight line.

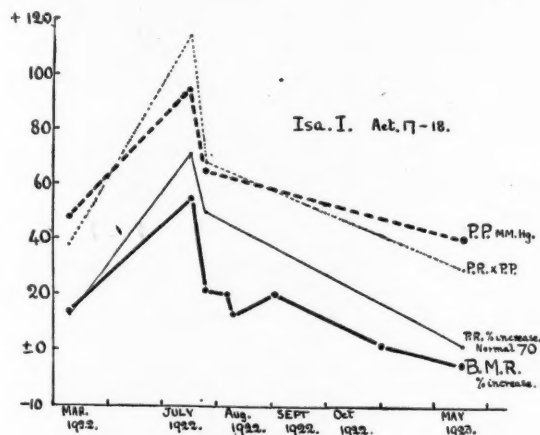


FIG. 3.

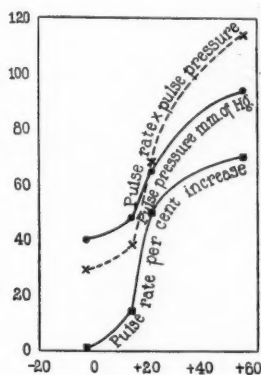


FIG. 4.

In view of these findings, when we turn back to the data shown in Fig. 2, we find a similar though less marked tendency towards a double-bended curve for pulse-pressure plotted against the basal metabolic rate. Thus in the portion of the curve from - 40 per cent. to + 20 per cent. the slope is much less steep than in that portion between + 20 and 70. After the latter point the curve tends to flatten out again. At present it is somewhat difficult to interpret the meaning of this finding, but it is probable that a study of pulse-rate, pulse-pressure, and general circulation rate in normal individuals subjected to varying degrees of increased metabolism resulting from muscular work might throw some light upon the question.

A further interesting point with regard to the case of I. I. is that the respiratory quotient varied in a very close inverse relationship to the basal metabolic rate. By adopting a suitable scale of ordinates it is possible to plot a curve for the respiratory quotient which is almost the mirror image of that for the basal metabolic rate. This has probably a very simple explanation. A normal individual undergoing starvation shows a fall of the respiratory quotient. Owing to the higher rate of metabolism this fall will be more rapid in individuals with hyperthyroidism. Moreover, there is evidence that the latter subjects have a smaller reserve of glycogen. Consequently in a given period of fasting,

usually from 7 p.m. until 9 a.m. on the following morning, the fall in the respiratory quotient will depend very closely upon the increase in metabolic rate.

In Figs. 5 and 6 there are plotted results obtained in two somewhat more complicated cases. These two cases were clinically very similar. Both were rather long-standing cases of hyperplastic goitre with all the classical signs. Both showed a remission during the period in which they were under observation.

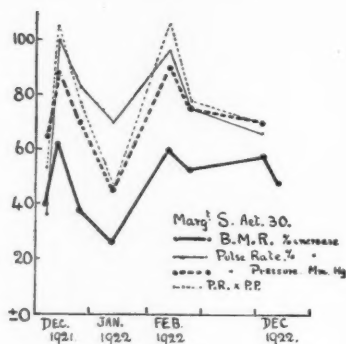


FIG. 5.

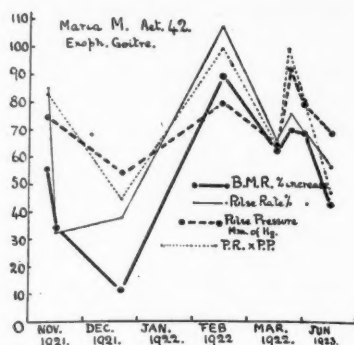


FIG. 6.

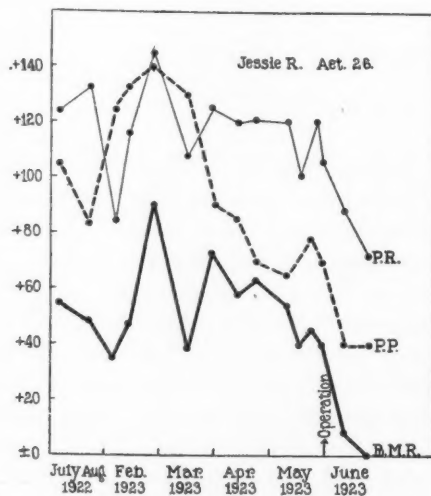


FIG. 7.

Both had a moderate increase of systolic blood-pressure, and evidence of cardiovascular disturbance as shown by cardiac irregularity from time to time. Unfortunately at the time no electro-cardiographic records were taken, and we are unable to state precisely the nature of the irregularity. Further details are given in the table and clinical summary at the end of the paper. In these two cases there was a fair general correspondence between the basal metabolic

rate and pulse-pressure, but it did not show the same relationship as we have pointed out in the case of I. I. It is probable that the high systolic pressure and the cardiac irregularity may account for this difference.

Figs. 7 and 8 show the findings in two cases which were treated surgically. The detailed findings are given in the table and clinical summary. The case of J. R. is interesting in many respects, and has been already referred to (p. 40). During the period February and March 1923 she suffered from various septic complications, and these apparently caused a disturbance of the relationship between the basal metabolic rate and pulse-pressure. For several days before operation she was given Lugol's solution, which seemed to cause a further disturbance of the relationship. After operation there was an immediate fall of pulse-

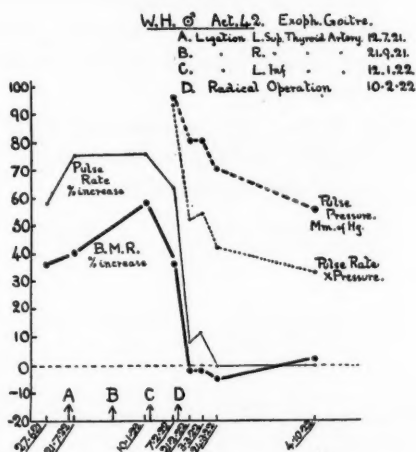


FIG. 8.

pressure parallel with that of the basal metabolic rate, and in this respect the case differs from that of W. H. (Fig. 8), where the metabolism fell immediately to normal, while the pulse-pressure fell more gradually. The explanation of this difference probably lies in the greater age and longer duration of the disease in the case of W. H.

In the table at the end of this paper we give the detailed findings of these and a number of other cases. The other cases are not shown graphically for the reasons that they are very similar to the above cases, and limitations of space render further diagrams impossible. In another section are given the clinical notes of all cases in which we have made serial observations of the basal metabolic rate and pulse-pressure.

*Summary of Conclusions.*

Increase of pulse-pressure is characteristic of and a constituent of the group of signs and symptoms known as hyperthyroidism.

Diminution of pulse-pressure is characteristic of uncomplicated hypothyroidism.

Pulse-pressure and basal metabolic rate therefore vary in the same direction.

Analysis of the findings in the 150 observations on pulse-pressure and basal metabolic rate shows a considerable degree of correlation between these two factors in cases of normal and disordered thyroid function.

A considerable amount of further work is necessary before the reasons can be given fully for this relation between pulse-pressure and basal metabolic rate.

Various complicating factors may disturb the relationship, but the measurement of the pulse-pressure is nevertheless a simple means for controlling the findings of the basal metabolic rate.

Serial measurements of the pulse-pressure made from time to time under basal conditions in cases of disordered thyroid function give important data that are easily recorded and interpreted for clinical purposes.

## II

The following table (pp. 47-53) is a record of 138 complete consecutive observations on thyroid cases.

In some of the cases thirty-one additional incomplete observations are given, chiefly as information regarding their progress.

There are twenty-three other consecutive observations in normals, in cases not diagnosed, and in a few other disorders, such as Fröhlich, dystrophy, infantilism, &c.

TABLE I.

Case No.	Sex and Age.	Date.	Diagnosis.	R. Q.	B. M. R.	Pulse.	S. B. P.	D. B. P.	P. P.	Remarks.
1	F. 17	19. 5.21	Goitre with hyperthyroidism, duration 2 years	—	—	—	118	60	—	Not basal conditions
		26. 5.21		—	-10	—	—	—	—	Sent home—to take cod-liver oil and tincture of iodine
		31. 5.21		—	-19	—	—	—	—	
		10. 3.22		—	—	—	—	—	—	
		18. 7.22		0.79	+14	79	128	80	48	
		26. 7.22		0.74	+55	120	135	40	95	
		7. 8.22		0.75	+22	105	120	55	65	Rest in bed, and digitalis
		8. 8.22		—	+20	—	—	—	—	
		1. 9.22		—	+13	—	—	—	—	Rest in bed, and digitalis
		3.11.22		—	+20	—	—	—	—	
2	F. 30	16. 5.23	Exophthalmic goitre	—	+2	72	123	83	40	
		12.12.21		0.99	+40	82	160	95	65	
		14.12.21		0.73	+62	120	185	97	88	
		23.12.21		0.78	+88	110	155	85	70	
		12. 1.22		0.81	+27	102	135	90	45	
		14. 2.22		0.72	+60	118	160	70	90	
		22. 2.22		0.75	+53	105	150	75	75	
		5.12.22		0.75	+58	100	135	65	70	
		14.12.22		0.75	+48	81	150	—	—	Rebreathing from bag; no clinical improvement
		22.12.22		0.76	+15	89	125	60	65	
3	F. 42	11.11.21	Hyperthyroidism with exophthalmos	0.77	+54	111	160	85	75	B. P. not under basal conditions
		16.11.21		0.80	+34	80	—	—	—	15.11.21. 8 st. 8 lb.
		6.12.21		—	-8	—	—	—	—	18.11.21. Tincture of iodine
		21.12.21		0.90	+11	83	145	90	55	27.11.21. S. 130. D. 70. P. P. 60
		14. 2.22		0.71	+90	125	150	70	80	
		18. 3.22		0.73	+63	100	130	65	65	
		26. 3.22		0.78	+71	106	148	55	93	22.12.21. Tincture of iodine continued to this date and beyond
		31. 3.22		0.78	+70	102	140	60	80	24.12.21. 9 st. 6 lb.
		20. 6.23		0.88	+44	95	160	90	70	





8	F. 19	7.12.22 27.12.22	Exophthalmic goitre	0.75 0.73	+77 +79	148 132	135 125	? 0 ? 10	? 115	Died suddenly 5 days later
9	F. 45	9.11.23 20.11.22	Adenomatous cyst, right lobe of thyroid	0.71 0.75	- 7 - 6	80 82	135 115	100 75	35 40	
10	F. 22	12. 1.23 13. 1.23 18. 2.23 27. 2.23 31. 5.23	Exophthalmic goitre Tetany	0.70 0.70 0.74 0.78 0.75	+39 +46 +36 - 5 + 5	114 113 97 98 104	112 112 120 100 98	50 60 60 ? 40 82	62 52 — 40 16	Following operation
11	F. 44 45	1. 3.22 12. 1.23 29. 1.23 7. 3.23 16. 5.23	Toxic adenoma	0.73 0.70 0.76 0.83 0.74	- 4 +40 +22 - 3 +28	79 100 88 77 70	165 162 145 120 140	85 80 70 80 95	80 82 75 40 45	
12	F. 30	19. 2.23 8. 3.23	Exophthalmic goitre	0.72 0.79	+56 +30	106 140	110 120	50 58	60 62	
13	F. 22	18.11.21 7.12.21	Simple goitre	0.78 0.92	+11 - 2	80 70	140 115	90 85	50 30	
14	F. 33	17. 7.22 19. 7.22	Exophthalmic goitre	0.77 0.77	+45 +36	92 87	125 110	55 55	70 55	
15	F. 29	10. 9.21 23. 9.21 27.10.21 9.11.21 16.12.21 14. 2.22 16. 5.22 4. 7.22	" " "	0.74 0.85 0.77 0.82 0.73 0.74 0.78 0.90	+56 +22 +24 +22 +18 +22 0 -16	117 110 92 85 94 99 87 80	115	95	60	
16	M. 41	7. 3.22 8. 3.22	Myotonia atrophica	0.66 0.76	-30 -23	61 60	80 83	60 55	20 28	Post-operative
17	F. 26	28.12.12 30.12.22	Adiposity	0.73 0.76	+ 8 - 3	65 64	108 105	70 60	38 45	Thyroid treatment on 3.1.23, gr. iii. t.i.d. X-ray of sella shows clinoids not clear

Case No.	Sex and Age	Date.	Diagnosis.	R. Q.	B. M. R.	Pulse.	S. B. P.	D. B. P.	P. P.	Remarks.
18	M. 19	11. 5.22 30. 5.22 14. 6.22 24. 6.22	Exophthalmic goitre, duration 1 year	0.77 0.80 0.91 0.87	+57 +49 +15 +26	101 84 84 100	115 118 105	45 50 50	70 68 55	8.5.22. S. B. P. 140. D. 90. P. P. 50 15.5.22. S. B. P. 130. D. 80. P. P. 50 15.6.22. S. B. P. 130. D. 60. P. P. 70 Losing weight till this date 21.6.22 gained 6 lb. in week 28.6.22 " 2 " 5.7.22 " 3 1/4 "
19	F. 17 1/2	23. 5.22 12. 7.22	Post-operative myxo- oedema, operation on thyroid when 7 and 15 years, removing first right and then left lobes	0.79 0.84	-40 + 7	80 90	105 ? 112	— 55	— 57	2.6.22 thyroid treatment begun 22.6.22 pulse getting more regular 28.6.22 S. B. P. 170. D. 70. P. P. 40 30.6.22. B.M.R. + 100 6.7.22. " +20 17.8.22. " +9
20	F. 64	9. 3.22 17. 5.22 8. 6.22	Post-operative thyroid- ectomy	0.73 0.81 0.81	+ 5 -23 -25	78 66 64	175	105	70	
21	F. 37	9. 5.22 15. 5.22 1. 6.22 12. 6.22 21. 6.22 26. 6.22 5. 7.22 26. 7.22	Toxic adenoma, thy- roid	0.78 0.84 0.83 0.77 0.79 0.79 0.78 0.78	+75 +42 +47 +75 +60 +69 +90 +63	77 96 126 147 132 107 129	160 140 Fibrillation 170	55 65 40	105 75 130	
22	F. 45	2. 6.23 15. 6.23 2. 7.23 9. 7.23	Toxic adenoma	0.71 0.77 0.71 0.80	+61 +39 + 6 + 0	122 104 59 57	135 110 140 115	70 70 80 75	65 40 60 40	
23	F. 35	3. 4.23 13. 6.23	Exophthalmic goitre (personae)	0.85 0.68	+33 +55	97 118	120 130	60 55	60 25	



Case No.	Sex and Age.	Date.	Diagnosis.	R. Q.	B. M. R.	Pulse.	S. B. P.	D. B. P.	P. P.	Remarks.
39	F. 19	16. 9.22	Exophthalmic goitre	0.76	-14	100	125	55	70	7 years' duration. Large goitre; palpitation; exophthalmos
40	M. 51	23. 9.22	Goitre with hyperthyroidism 18 days after operation	0.76	-12	104	145	75	70	
41	F. 50	4.10.22	Myxoedema	0.73	-23	66	145	80	65	
42	F. 56	18.12.22	?	0.78	-14	62	125	80	45	
43	F. 10	2. 1.23	Tonsillitis	0.84	-14	54	96	55	41	
44	M. 45	9. 1.23	Exophthalmic goitre	0.75	-9	82	118	58	60	Clinically this seemed to be a case of moderately intense hyperthyroidism of 4 months' duration
45	F. 56	10. 2.23	Myxoedema	0.81	-36	78	143	105	38	
46	M. 25	19. 2.23	? Hysteria	0.83	-10	66	90	60	30	
47	M. 9	29. 3.23	Fröhlich	0.76	-28	80	130	80	50	
48	F. 34	22.12.21	Goitre	0.73	+27	116	115	60	55	
49	M. 21	24. 2.22	Keratoconus	0.77	+5	84	123	70	53	
50	F. 39	23. 3.22	Hyperthyroidism	0.79	+12	82	115	70	45	
51	F. 39	11. 4.22	—	0.79	+15	95	135	75	60	
52	F. 44	26. 5.22	Goitre, parenchymatous	0.83	+24	109	125	75	50	
53	F. 20	3. 6.22	Delayed development	0.84	+19	80	125	75	50	
54	F. 24	6. 6.22	Hyperthyroidism	0.77	+50	100	142	78	64	
55	F. 50	6. 6.22	?	0.85	+2	83	115	70	45	
56	F. 30	18. 6.22	Uraemia	0.74	+17	80	112	63	44	
57	F. 24	23. 6.22	Hyperthyroidism	0.77	+15	109	120	63	57	
58	F. 31	29. 5.22	Exophthalmic goitre	0.92	+23	108	135	87	48	
59	F. 64	9. 3.22	Post-operative thyroidectomy	0.73	+5	78	175	105	70	
60	F. 42	13. 9.22	Exophthalmic goitre	0.84	+14	77	101	65	36	
61	F. 19	15. 9.22	Hyperthyroidism	0.81	+32	125	140	40	100	
62	M. 31	28. 7.22	? Neurasthenia	0.85	+18	60	102	65	37	

63	F. 17	21. 9.22	Hyperthyroidism	0.82	+ 39	117	123	50	53	No post-mortem evidence of thyroid disease. Bronchitis. Pott's disease of spine. The basal metabolic rate is extremely doubtful owing to the great deformity invalidating the Dubois body-surface formula
64	F. 28	19. 9.22	Goitre	0.81	+ 34	96	150	85	65	
65	F. 45	26. 9.22	Goitre, parenchymatous	0.79	+ 13	86	140	75	65	
66	F. 34	9.10.22	—	0.78	+ 18	84	130	80	50	
67	F. 23	15.11.22	Hyperthyroidism	0.76	+ 24	122	142	70	72	
68	F. 23	17.11.22	Exophthalmic goitre	0.75	+ 61	106	135	60	75	
69	F. 22	18.11.22	Adenoma of isthmus of thyroid	0.73	+ 27	95	128	60	68	
70	F. 62	13.12.22	Exophthalmic goitre	0.72	+ 76	123	150	75	75	
71	F. 23	15.12.22	"	0.74	+ 68	121	120	50	70	
72	F. 22	19.12.22	Hypopituitarism	0.76	+ 6	70	125	98	27	
73	F. 32	20.12.22	Arthritis deformans	0.95	+ 24	74	108	78	30	Operation and death next day
74	F. 38	21.12.22	Hyperthyroidism	0.70	+ 21	96	125	90	35	
75	M. 43	13. 1.23	? Hyperthyroidism ? Adenoma of thyroid	0.82	+ 26	86	110	80	30	
76	F. 33	30. 1.23	Thyroidism	0.75	+ 2	61	105	60	55	
77	F. 27	1. 2.23	Exophthalmic goitre	0.72	+ 41	119	120	75	45	
78	F. 36	6. 2.23	Obesity	0.78	+ 3	74	120	80	40	
79	F. 68	8. 3.23	Toxic adenoma	0.82	+ 45	102	180	90	90	
80	F. 26	14. 3.23	Exophthalmic goitre	0.78	+ 55	126	135	45	90	
81	F. 21	20. 3.23	Adiposity	0.74	+ 2	63	125	90	35	
82	F. 44	20. 3.23	Exophthalmic goitre	0.76	+ 76	115	150	70	80	
83	F. 19	26. 3.23	"	0.80	+ 97	91	120	55	65	Recent very mild case
84	M. 20	28.11.21	Normal	0.84	0	71	105	85	20	
85	M. 12	29. 5.22	Goitre	0.84	0	106	100	70	30	
86	F. 54	21.11.22	Myxoedema	0.67	0	84	123	90	43	
87	F. 13	28.11.22	Large simple goitre	0.77	0	94	100	50	50	
88	F. 18	17. 2.23	Exophthalmic goitre	0.76	1	88	120	60	60	

## III

*Case 1.* I. I., female, aged 17. Admitted 19.5.21. *Complaint:* swelling of neck, shortness of breath. *Duration:* two years.

One sister, when young, had slight swelling of the thyroid. Patient was not nervous. There were no tremors and no exophthalmos. The signs of Stellwag, Von Graefe, and Moebius were absent. The thyroid gland was considerably enlarged, slightly more on the right side; isthmus much enlarged. She appeared to be in good health and there was no dyspnoea while she was in bed. Pulse 60. Heart sounds closed.

When discharged on 6.6.21 she was advised to take cod-liver oil and tincture of iodine.

Readmitted with marked tachycardia, exophthalmos fairly well marked, slight enlargement of the thyroid, and fine tremor. She was kept at rest in bed and the basal metabolic rate gradually fell.

Case is discussed in some detail in Part I. See also Figs. 3 and 4.

*Case 2.* M. S., female, aged 30. Admitted 29.11.21. Exophthalmic goitre. *Complaint:* soreness of right eye. *Duration:* one month.

Large thyroid, exophthalmos marked, Von Graefe sign present. Faint pulsation in thyroid, with humming murmur. Joffroy sign present. Pulse 96. Slight blowing mitral murmur. Sweating of hands and feet. Fine tremor of fingers, tongue, and legs. The evidences of hyperthyroidism were first obtained in 1912. After some worry at home, in September 1921, she became thinner and the prominence of the neck and eyes was noticed by her friends. She had palpitation and was easily tired. The exophthalmos had been present for nine years with very little variation in degree. From 3.12.21 till her discharge on 22.1.22 she had tincture of iodine, the dose being gradually increased from 3 to 15 minims thrice daily and then reduced. Radium was applied on 14 and 28.2.22.

On 2.12.22 she was readmitted with a more marked degree of exophthalmos, the thyroid symmetrically more enlarged and giving a slight thrill. See also Fig. 5.

*Case 3.* M. M., female, aged 42. Admitted 9.11.21. *Complaint:* shaking, excessive sweating. *Duration:* five years.

Tremors, prominence of the eyes, feeling tired. One sister had goitre, with prominent eyes and nervousness. There was no obvious enlargement of the thyroid, but there was a slight fullness in that region. General appearance was slightly anxious. Pulse 100; regular. Slight episternal and carotid pulsation. No heart murmurs, except a fine blowing aortic systolic. Von Graefe sign positive. Palpebral fissure wider than normal, but no exophthalmos. Convergence good.

She was sent home in December 1921 with a prescription for KI, and she returned on 13.2.22, when the basal metabolic rate was 90 per cent., and pulse 125. The thyroid is now palpable. Systolic mitral murmur present.

Iodine stopped.

Readmitted for three weeks in March 1922, and again in June 1923. See also Fig. 6.

*Case 4.* J. R., female, aged 26. Admitted 22.7.22. Exophthalmic goitre. *Complaint:* swelling of neck, nervousness. *Duration:* eight months.

Considerable enlargement of thyroid, especially the right lobe. The gland was of uniform firm consistence. There was a distinct thrill through the right lobe. Occasional palpitation and dyspnoea. Pulse 124; regular in time, but varying in force. Both sounds of the heart were impure in all areas. The apex



was four inches from the mid sternal line in the 5th space. Restless worried appearance. Flushed and emaciated. Slight exophthalmos. Von Graefe and Stellwag signs present. Fine tremor of fingers. Wassermann negative. She was kept in bed for about a fortnight, pulse remaining about 110. The French tincture of iodine,  $\mathcal{Q}$  3, thrice daily, was given. General improvement occurred with a fall of the pulse-rate.

She was discharged from hospital in September and readmitted on 31.1.23. She had greatly improved and had no attacks of nervousness. During March, April, and May she had tonsillitis several times and septic onychia while in the ward. These septic conditions led to considerable variations in the basal metabolic rate, but this on the whole remained at a fairly high level.

On 11.5.23 patient was put on Lugol's solution,  $\mathcal{Q}$  x t.i.d., in order to see what variation would occur in the basal metabolic rate and vascular thrill. This dose was continued for three days—then increased to  $\mathcal{Q}$  xv for two days—then stopped. At the end of that time the basic metabolic rate was considerably reduced and arterial thrills over the thyroid had completely disappeared. Seven days after stopping the administration of Lugol's solution definite return of the thyroid thrill was evident, with increase of the basal metabolic rate. This solution was begun again on 23.5.23 in order to prepare the patient for operation. Operation on 30.5.23. About six-sevenths of each lobe were removed along with the isthmus.

Some points in this case are discussed in Part I. See also Fig. 7.

*Case 5.* W. H., male, aged 42. Admitted 26.5.21. *Complaint:* weakness and general debility; diarrhoea, flatulence, and intestinal colic. *Duration:* twenty-seven years.

The diarrhoea started suddenly, accompanied by griping pains. The attacks lasted for a month or six weeks at a time. This was the fourth attack. He felt in good health between attacks. He had had the present attack since October 1920 and had had an increasing feeling of debility, causing him to report sick. Since October 1920 he had lost two stones in weight. He was of a nervous disposition. He was a rather sparely built man with anxious expression. There was some exophthalmos, anaemia, and a fine tremor of the hands. Sweating all over the body. The thyroid was enlarged. A distinct throbbing was visible and thrill palpable over the thyroid. Pulse 90; marked pulsation at the root of the neck. Von Graefe sign slight. He had his appendix removed in 1905 without beneficial result.

Operation 12.7.21. Ligature of superior thyroid vessels on left side.

Operation 21.9.21. A similar operation on right side. He had already gained 6 lb. in weight.

On 9.10.21 there was a recurrence of the diarrhoea.

On 20.12.21 readmitted, showing no clinical improvement. Pulse 120. Thrill all over the thyroid. Fine tremor of hands. Operation 10.2.22. Intra-capsular resection of greater part of both lobes and isthmus of thyroid. Histologically no colloid was to be seen in thyroid tissue. Cells tall. Areas showed degeneration, with here and there lymph nodes, some with germinal centres. Hyperplastic goitre. Patient rapidly gained in weight after operation. See also Fig. 8.

*Case 6.* E. S., female, aged 31. Admitted 18.3.21. Lingual thyroid removed on account of obstruction on 14.1.21. *Complaint:* Hoarseness. *Duration:* ten years with remissions.

No visible or palpable neck swelling. Moebius and Von Graefe negative. Patient thinner, with dyspnoea, palpitation, but with no exophthalmos. The skin had become dryer and the hair had been falling out considerably of late.

*Diagnosis:* post-operative myxoedema. From April to October 1921

thyroid treatment with intervals. On 10.2.22 two pieces, measuring each 2 cm. x 1.5 cm., of thyroid tissue obtained from a case of Graves's disease were grafted in the abdominal wall.

28.4.22. A note from her doctor stated that she showed well-marked signs of myxoedema, with swelling of face and hands, thick speech, and constipation.

*Case 8.* I. McB., female, aged 19. Admitted 31.10.22. Acute exophthalmic goitre. *Complaint:* swelling in neck, prominent eyes, and nervousness since March, when she had an attack of influenza. *Duration:* seven months.

This case was a typical case of acute Graves's disease with large pulsating goitre, very marked tremors, exophthalmos, and extreme tachycardia. She died suddenly on getting up against orders, and the post-mortem findings were in every respect typical.

*Case 10.* E. R., female, aged 22. Admitted 24.2.21. Adenomatous goitre. *Complaint:* swelling of neck. *Duration:* eight years.

The swelling had not increased in size. Two years before the eyes became more prominent and she began to feel nervous, breathless, and to suffer from palpitation. She had experienced difficulty in swallowing for the last three months. She had not lost weight.

There was a slight enlargement of each lobe of the thyroid. It was fairly firm, with small irregularities. Tremors of the fingers and pulsation of the neck marked. Pulse 100; regular. Rough blowing systolic murmur at the mitral area propagated to the axilla. Slight systolic murmur in the other areas. Signs of consolidation at the right apex. Many teeth were in a bad state. Pupils dilated. Joffroy sign present. Slight impairment of convergence.

Operation by Sir Harold Stiles on 16.3.21.

The greater part of the left lobe of the thyroid was removed. Discharged 4.4.21. Readmitted 9.1.23 to Sir Harold Stiles's ward. She was a very nervous woman with marked exophthalmos. Von Graefe sign positive. Fine tremor of both hands. Pulse 100; regular. A firm enlargement of the thyroid practically confined to the right lobe. No thrill felt, but a bruit on auscultation over the thyroid.

Operation on 7.2.23 by Sir Harold Stiles. Five-sixths of the right lobe were removed.

On 13.2.23 she woke with a swollen face and with hands in a position of palmar flexion of wrists and metacarpo-phalangeal joints and extension of the interphalangeal joints.

Marked facial reflex. The administration of parathyroid, gr. 1/100, morning and night, was followed by improvement of symptoms.

17.2.23. Chvostek sign very marked. Trousseau sign positive. Knee-jerks were difficult to obtain owing to cramp. Severe attack of tetany on 22.2.23. There was great difficulty in swallowing.

Discharged 31.5.23. Readmitted 26.6.23.

*Case 11.* E. S., female, aged 44. Admitted 27.2.22. Toxic adenoma. *Complaint:* swelling in front of neck, palpitation at night. *Duration:* five years.

The swelling was at first small and uniform. During the last six months it had increased in size. No exophthalmos or visual symptoms at any time. During the last month slight myalgic pains down the right side of the neck, becoming worse and constant. She was rather pale, but did not seem nervous.

There was a rounded enlargement in the front of the neck, extending over both sides, firm in consistence and pulsating. The overlying skin was movable and not discoloured. Heart not enlarged. Pulse 68; regular. Von Graefe absent.

Operation by Sir Harold Stiles on 17.1.23.

*Case 13.* A. E., female, aged 22. Admitted 15.11.21. Simple goitre. *Complaint:* swelling of the neck. *Duration:* twelve years.

General health always good, the swelling being unaccompanied by symptoms. At one time internal iodine treatment caused the apparent disappearance of the swelling, but it reappeared when she began hard work on a farm. She had slight palpitation on exertion and a choking feeling at the root of the neck. No other inhabitant of the district of Blackbraes, where the farm is, had goitre except her mother and four brothers, all of whom had goitre.

There was a definite almost uniform swelling of the thyroid, elastic in consistence. No separate nodules felt. Pulse 90; regular. Tension high, 140-90. Heart apex in nipple-line. Faint mitral systolic murmur, heard also at base. Urine contained at times a trace of sugar. Respiratory, alimentary, and nervous systems normal. Menstrual history normal. She was given increasing doses of tincture of iodine, from three to fifteen minims, while she was in hospital. She worked in the ward most of the time and put on 12 lb. in weight. The thyroid seemed softer and smaller, and patient felt much stronger on discharge.

*Case 14.* H. McC., female, aged 33. Admitted 13.7.22. *Complaint:* headache, nervousness, swelling of the neck, prominence of the eyes. *Duration:* four years.

She had recently been losing weight. The nervousness was apparent. Exophthalmos not very marked. The swelling of the thyroid was uniform and pulsating. Fine tremor of the fingers. Pulse 100; regular. Heart did not appear to be enlarged. Treatment by rest in bed for some weeks. The exophthalmos became less marked and the pulse less frequent.

On 31.8.22 the tonsils and adenoids were removed.

The basal metabolic rate fell considerably while she was under treatment.

*Case 15.* M. W., female, aged 29. Admitted 7.9.21. Exophthalmic goitre. *Complaint:* exhaustion; protruding eyes. *Duration:* six years.

Breathlessness and throbbing increased by work. She had become nervous. She spoke with a husky voice. She sweated a great deal and felt hot. The eyes were greatly protruded. Von Graefe sign positive. Converged with great difficulty. The thyroid gland was slightly enlarged—chiefly the left lobe. Tonsils both enlarged. Sugar was present in the urine on several occasions and diacetic acid on one day. She suffered from constipation. Palpitation two months before admission. Pulse 100-120. In all areas the heart sounds were closed. The heart was not enlarged. Fine tremor on extending arms and fingers.

Discharged on 16.11.21. Throughout October and November she had iodine,  $\alpha$  3-7, t.i.d.

Operation by Sir Harold Stiles in May 1922.

*Case 18.* J. A., male, aged 19. Admitted 8.5.22. Exophthalmic goitre. *Complaint:* sweating, nervousness, prominence of eyes. *Duration:* one year.

Worry associated with his work appeared to have brought on the symptoms. At first there was considerable swelling of the neck, but this had to a large extent disappeared. He was very easily excited and on occasion had tremors of the legs and hands. At present there was slight prominence of the eyes, but there was no visible enlargement of the thyroid. Pulse 90; regular. Heart not enlarged. Sounds closed. *Bruit de diable*. Von Graefe, Stellwag, Moebius, and Joffroy are positive. Skin moist and warm. Wassermann negative.

*Case 19.* M. L., female, aged 17½. Admitted 20.5.22. Post-operative myxoedema. *Complaint:* breathlessness; delayed onset of puberty.

She had partial thyroidectomy at the age of 7, the right lobe being removed.

Apparently it had been considerably enlarged by parenchymatous goitre. At the age of 15 years the greater part of the left lobe was removed, although there was not much enlargement at this time. She ceased to grow since the date of the last operation. She had not yet menstruated. Two brothers had thyroid enlargement and one had had an operation on the thyroid.

General appearance: features coarse; lips thick; nose stubby; malar flush; skin dry; speech slow; intelligence below par. Mental processes much delayed; hands thick, short, and fat. Breasts full, but nipple not well marked. She had a small appetite; tongue dry. Teeth fairly healthy. Distinct dullness of abdomen. Large mass, regular in shape, hard, extending apparently up out of pelvis as far as 1 in. below umbilicus. Dull on percussion, slightly tender, movable from side to side. A few scanty hairs on the pubic region.

Otherwise nervous system and the heart and lungs normal.

Under thyroid administration, patient improved and the pulse-rate gradually increased to 100 from 70. The skin became less coarse and less dry and the mentality became brighter. The Wassermann test was negative.

Thyroid treatment was begun on 2.6.22, reaching a maximum dosage on 22.6.22, when she was having 9 gr. thyroid extract daily.

*Case 21.* C. W., female, aged 37. Admitted 5.5.22. Exophthalmic goitre. *Complaint*: nervousness, prominence of eyes, weakness, palpitation, and breathlessness. *Duration*: five years.

Nervousness since childhood; she began to lose weight five years ago. She attributed this to worry associated with the death of her mother and to domestic financial troubles during the war. The swelling of the thyroid and prominence of the eyes developed about a year later. Three years ago she was in Chalmers Hospital, Edinburgh, for a month, and benefited sufficiently to enable her to carry on at home fairly well. During the last two years she had suffered from weakness and lethargy. Palpitation began 18 months ago, associated with breathlessness. She had had no important previous illnesses. The family history was good. Definite exophthalmos and enlargement of the thyroid. Pulse 116; regular. Vessel wall not thickened. Heart sounds closed in all areas. *Bruit de diable* was well heard. Attacks of vomiting and diarrhoea during the last year. Von Graefe, Stellwag, and Joffroy present; Moebius absent.

*Case 22.* E. R., female, aged 45. Admitted 31.5.23. Toxic adenoma of thyroid. *Complaint*: pain across upper part of stomach, headaches, severe sweatings, loss of strength and weight. *Duration*: two years.

She was nervous and slept badly. Before admission she was informed there was sugar in the urine. Until marriage, five years ago, she was a healthy woman. No goitre in her family. Her disclaimer of any disharmony in domestic relations did not seem very cordial. A spare woman, complexion healthy looking. Was restless, fidgeting constantly with her hands throughout the interrogatory examination. Hands tremulous during movements. Possibly slight exophthalmos. She often had palpitation and was breathless on climbing. Pulse 116; regular. Vessel wall palpable. Conspicuous pulsation in arteries of the neck—an obvious symmetrical swelling of the thyroid gland. Diffuse heaving pulsation in 3rd, 4th, and 5th spaces, extending to nipple line. No thrill. A faint systolic bruit at aortic and pulmonary regions and a loud systolic bruit over thyroid. Spleen just palpable with deep respiration. Sugar in urine on three occasions. Sp. gr. 1.016. No albumin. Von Graefe sign present. A constant fine tremor when arms were extended. Transferred to Sir Harold Stiles's ward on 21.6.23 for operation.

Lugol's iodine,  $\alpha$  xv t.i.d., for four days previously; not any perceptible change noted.

Readmitted for night of 8-9.7.23.

*Case 23.* E. B., female, aged 35. Admitted 27.3.23. *Complaint:* strained feeling in eyes and a dragging of the lids. *Duration:* three weeks.

Swelling of the neck was first noticed at this period and severe palpitation, mostly at night, when the patient was trying to get to sleep. Sweating and flushing more marked than normal. She had been more nervous during the past three months, and thinner during the past nine months. Her work was of a harassing nature. The thyroid was symmetrically enlarged, firm with faint thrill on palpation, but no bruit on auscultation. Pulse 108; regular. Vessel wall not thickened. Heart sounds closed and heart not enlarged. Von Graefe and Stellwag negative. Sweating, flushing, and exophthalmos hardly appreciable. Tremor in tongue, fingers, and feet. Wassermann negative.

Discharged on 5.4.23.

Readmitted on 11.6.23.

Soft uniform elastic enlargement of the thyroid, of moderate degree, without thrill, but with transmitted pulsation. No heart bruit, except pulmonary systolic. Soft systolic bruit over thyroid. Slight Von Graefe, slight exophthalmos. Trace of sugar in urine.

Transferred to Ward 7 on 24.7.23.

She had had  $\alpha$  xv Lugol's solution since 21.7.23.

Operation, 25.7.23. About one-eighth of the right lobe and one-sixth of the left lobe were left.

*Case 24.* H. V., female, aged 25. Admitted 18.4.23. Exophthalmic goitre. *Complaint:* weakness, breathlessness, swelling in throat. *Duration:* nine months.

There was no loss of weight or flushing. On examination, however, there was slight flushing of face and forehead. Exophthalmos not present. The other eye signs were also negative. Slight tremors of the fingers and eyelids. Thyroid was symmetrically enlarged to a slight extent. It was soft and elastic, with systolic thrill and murmur. Marked carotid pulsation. Extensive itchy urticarial rash on body and limbs. Pulse 100; regular. Heart not enlarged. A soft systolic murmur in all areas. Tonsils enlarged, with deep crypts. No glycosuria.

Lugol's solution,  $\alpha$  x t.i.d., from 11.5.23, followed by symptomatic improvement. Carious teeth extracted 6.6.23.

Operation by Sir Harold Stiles on 7.6.23. About half of the right lobe and the greater portion of the left lobe were removed.



TABLE II. *Basal Metabolic Rate.*

	-40 to -30	-30 to -20	-20 to -10	-10 to 0	0 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	70 to 80	80 to 90	90 to 100	No. of Observa- tions.	Aver- age B.M.R.
20-30	1½	2	2½	1	1½	—	—	—	—	—	—	—	—	—	8½	-16.2
30-40	1½	—	5½	5½	1½	2	1	1	—	—	—	—	—	—	18	-4.7
40-50	—	—	4	7½	3½	5	5	1	2	—	—	—	—	—	28½	9
50-60	—	—	1	1½	6	4½	4	3	1	1½	—	—	—	—	21	17.1
60-70	—	1	1	1½	1½	3	5	4½	5½	3	2½	—	—	—	28½	30.2
70-80	—	—	1	1½	1	—	3	1½	3½	3½	2½	1½	1	1	18½	42.4
80-90	—	—	—	1	—	—	1	1½	2	1½	1½	1	1	—	9½	55.3
90-100	—	—	—	—	—	—	—	1½	1	2½	1	1	—	—	5½	52.7
100-110	—	—	—	—	—	—	—	—	—	1	—	1	—	—	2	60
110-120	—	—	—	—	—	—	—	—	—	—	1	1	—	—	1½	71.7
120-130	—	—	—	—	—	—	—	1½	—	—	1	—	—	—	2½	47
130-140	—	—	—	—	—	—	—	1	1	—	1½	1	1	1	4½	62.2
140-150	—	—	—	—	—	—	—	—	—	—	—	1	—	—	1	75
? over 150	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—
Number of observa- tions	3	3	14	19	15	15	18½	15½	15½	11½	9½	8½	1	1	150	—
Average pulse- pressure	30	38.3	39.1	46.8	49.5	50.7	58	75	63.6	78.3	91.3	104.5	110	110	—	—



# REFERENCES.

1. Read, *Journ. Amer. Med. Assoc.*, 1922, lxxviii. 1887.
2. Stewart, *The Harvey Lectures*, 1912-13, New York, 86.
3. Douglas and Haldane, *Journ. Physiol.*, Camb., 1922, lvi. 69.
4. Meakins, Dautrebande, and Fetter, *Heart*, Lond., 1923, x. 153.
5. Barcroft, Bock, and Roughton, *ibid.*, Lond., 1921, ix. 7.
6. Barcroft, Communication before Internat. Physiol. Congress, Edinburgh, 1923.
7. Sturgis and Tompkins, *Arch. Int. Med.*, Chicago, 1920, xxvi. 467.
8. Boothby, *Oxford Medicine*, New York, 1921, iii. 924.
9. Beall, *Journ. Amer. Med. Assoc.*, 1921, lxxvi. 1639.
10. Harris, *Brit. Med. Journ.*, 1923, i. 630.
11. Meakins and Davies, *Edinb. Med. Journ.*, 1922, N.S., xxxviii. 4.
12. Krogh, *Anatomy and Physiology of Capillaries*, New Haven, 1922, 158.

## SOME FACTORS CONCERNED IN THE AETIOLOGY OF TETANY IN CHILDREN

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### *Historical.*

IN 1901 Sabatini (1) demonstrated the importance of calcium in controlling the response of the cerebral cortex to stimulation. He showed that the addition of isotonic solutions of calcium chloride to the cortex reduced the response of the brain to mechanical and electrical stimulation, while substances known to precipitate calcium might even cause convulsions if present in sufficient concentration.

Quest (2) in 1905, recognizing that tetany in infants was frequently associated with rickets, a disease in which there was known to be a disturbance of calcium metabolism, emphasized the importance of Sabatini's work, and attempted to explain the increased nervous excitability in his cases of tetany by demonstrating a decrease in the calcium content of the brain. For this purpose he estimated and compared the amounts of lime in the dried brains of children with and without tetany, and found it diminished in the former. He, however, admits that his results were not conclusive.

In 1909 further confirmation of Sabatini's observations was supplied by the experimental work of MacCallum and Voegtlin (3). They observed that the tetany produced in dogs by parathyroidectomy was relieved by the administration of calcium salts. They further showed that the blood of parathyroidectomized dogs contained less calcium than the controls.

Later, MacCallum, Lambert, and Vogel (4) also showed that normal blood deprived of its dialysable calcium could produce hyperexcitability of the nerves in an amputated limb through which it was perfused. Meanwhile Cattaneo (5) and Longo (6) in Italy, and Neurath (7) in Germany, attempted to estimate the calcium content of the blood in idiopathic tetany. Large amounts of blood were necessary for the methods used by the Italian workers and their results are necessarily few and inconclusive. The figures obtained by Neurath show a relative calcium reduction in the cases of tetany, but as the method he used did

not permit of absolute figures, his results are not capable of comparison with those obtained by other methods.

In 1918 Howland and Marriott (8), having devised a technique for the estimation of calcium in small amounts of serum, concluded that in active tetany the calcium of the serum is invariably reduced. In eighteen cases of active tetany in infants they found the average calcium content of the serum to be 5.6 mg. per 100 c.c., while in five normal infants they found the calcium values to vary between 10 and 11 mg. The results of these investigators have since been largely confirmed by other workers. There is therefore strong *prima facie* evidence in favour of the view that the signs and symptoms of tetany are due directly to a fall in the blood calcium. If this is so, a low calcium should exist in every case of tetany, and tetany should exist whenever the calcium is low. Also, the severity of the tetany should vary directly with the degree of calcium reduction.

#### *Present Investigation.*

The present investigation was undertaken with a view to determining if these three points could be proved. We have also extended our observations to the study of the mode of action of the calcium salts in controlling the signs and symptoms of tetany.

For this purpose we have made observations on the calcium and phosphorus content of the blood-serum and on the alkaline reserve of the venous blood plasma in rachitic and non-rachitic infants and children who showed increased excitability of the peripheral nervous system.

#### *Methods.*

The calcium was estimated by the Kramer and Tisdall (9) method and the phosphorus by the Tisdall (10) method. The serum was separated immediately in every case. The figures for the alkaline reserve were obtained by means of the Van Slyke micro-apparatus (11). The estimations were always done immediately after the blood was withdrawn, and duplicates obtained in each instance. The figures quoted are at 0° C. and 760 mm. pressure.

The milliamperemeter which we employed to record the strength of the current used in examining the electrical excitability was frequently tested against one of known accuracy.

In the course of our investigations the difficulty of making an infallible diagnosis of latent tetany has been impressed upon us. In infants who present a combination of Chvostek's and Trousseau's signs with definite laryngismus there can be no doubt regarding the diagnosis. We have invariably considered them to be suffering from tetany in an active form. On the other hand, one meets cases which give a definite history of carpo-pedal spasm, but who have, when examined, only a Chvostek's sign: these, we think, must be regarded as

examples of latent tetany. Rachitic infants in whom no history of active tetany can be elicited, but who show a definite facial phenomenon, present the greatest difficulty in diagnosis. We are well aware that many observers rely on the electrical reactions (Erb's sign) to establish the diagnosis in such cases; our personal experience, however, has led us to place little reliance on this sign as a guide to diagnosis in doubtful cases. Also, little help can be gained from the published results of others so long as the present scarcity of definite information regarding the normal limits of variation exists.

Table I shows the electrical reactions of thirty-two children of varying ages whom we examined consecutively in the hospital wards. None of the children included were or had been suffering from tetany.

TABLE I.

Sex.	Age. Months.	Disease.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.*
M.	3	Feeding regulation	0.8	1.0	5.0+	5+	2.8
M.	5	Gastro-enteritis	0.3	1.1	1.7	5+	2.1
F.	6	Pneumonia	1.0	5.0+	5.0+	5+	5.0+
M.	8	Gastro-enteritis	0.4	2.0	1.8	5+	3.6
F.	9	Pneumonia	0.7	1.8	5.0+	5+	4.0
M.	10	Feeding regulation	1.0	1.4	5.0+	5+	5.0+
M.	11	Pneumonia	1.8	3.0	5.0+	5+	5.0+
F.	15	Dyspepsia	0.5	1.4	4.1	5+	3.0+
F.	17	Epilepsy	1.0	1.0	5.0+	5+	3.5
F.	18	Pneumonia	0.8	2.5	1.6	5+	3.8
M.	19	Pneumonia	1.2	2.0	2.5	5+	5.0+
M.	20	Rickets	0.9	1.0	2.6	5+	5.0+
M.	20	Tumour	0.9	0.8	1.4	5+	3.4
	Years.						
M.	2	Phthisis	0.4	0.5	2.0	5+	2.4
M.	2	Rickets	0.9	1.8	4.0	5+	5.0
M.	2	Rickets	1.0	1.7	1.7	5+	3.5
M.	2½	Rheumatism	1.6	2.5	5.0+	5+	5.0+
M.	3	Tuberculous adenitis	1.2	1.2	3.6	5+	3.6
M.	5	Cerebral tumour	0.7	1.3	5.0+	5+	3.4
F.	5	Nephritis	0.6	1.2	1.2	5+	3.0
M.	7	Rheumatism	1.2	1.8	3.0	5+	4.0
F.	7½	Conval. chorea	0.6	1.3	3.6	5+	3.8
F.	7½	Hysteria	0.8	1.9	1.4	5+	2.4
M.	8	Rheumatism	0.9	1.4	5.0+	5+	5.0
M.	8½	Conval. chorea	1.0	1.6	2.8	5+	4.0
M.	9	Pleurisy	0.8	1.4	1.2	5+	2.6
F.	10	Conval. chorea	0.7	0.9	1.0	5+	2.9
F.	10	Cyclical vomiting	0.3	1.7	0.8	5+	3.2
M.	10	Conval. chorea	0.8	1.3	5.0+	5+	2.5
M.	11	Rheumatism	1.6	1.4	3.6	5+	5.0+
M.	11	Rheumatism	0.6	1.0	1.5	5+	3.4
F.	13	Diabetes	0.9	2.5	5.0+	5+	3.5

\* Kathodal closing tetanus.

It is evident, even from this small series of results, that wide variation in the kathodal closing contraction may occur in infants and children without tetany. An anodal opening contraction obtained with less current than an anodal closing contraction and both with less than 5 ma. was found in five out of thirty-two cases. A kathodal opening contraction with less than 5 ma. was never found in a normal infant, but when found is undoubtedly indicative of tetany. We have frequently failed to find a K. O. C. with less than 5 ma., how-

ever, in cases in which the presence of other symptoms has convinced us of the existence of active tetany. It may be pointed out that we did not anaesthetize our patients, and that a kathodal opening contraction might have been obtained more frequently if this had been done. The amount of current used in no case exceeded 5 ma.

Details of the thirty-four cases studied have been recorded in Table II. It is an established fact that tetany and rickets are frequently associated, but that the severity of the former bears no relationship to the severity of the latter. Hence we have simply indicated the presence of rachitic changes (as determined radiologically) by means of a + sign.

The Chvostek sign or facial phenomenon (F.P.) we have recorded as follows:

- + = brow or mouth twitch only.
- + + = twitch at brow and nose, or at mouth and nose.
- + + + = twitch at all three places.

The presence of laryngismus and Trousseau's sign has been indicated by + or + + according to the severity of the condition.

*Existence of Tetany with a normal Calcium Content of the Serum.*

Referring to Table II it will be observed that of the twenty-four cases of three years and under who gave a positive Chvostek's sign, seven had a normal serum calcium. None of these at the time of examination showed signs of active tetany. With one exception they were all suffering from rickets, and we believe them to be cases of latent tetany. It will be noted that in every case showing signs of active tetany there was diminution of the serum calcium.

In only one of the children of over three years who manifested increased mechanical excitability was the calcium content diminished. This was R. D., admitted with late rickets and a positive Trousseau sign in addition to a facial phenomenon. The remaining nine cases all showed a normal calcium content in the presence of increased mechanical excitability. There is considerable doubt in our minds as to whether they should be looked upon as cases of latent tetany. We hope later to make a more detailed study of these cases.

That active tetany can occur with no change in the blood calcium is a fact well corroborated by others. It is perhaps best shown in the tetany produced experimentally by means of hyperpnoea. Collip and Backus (12) in 1920 demonstrated clearly the production of tetany in the human subject by this means. Grant and Goldman (13), working along the same lines, actually produced a convulsion in one instance. These last-mentioned authors showed that in this type of tetany there was actually a rise in the calcium content instead of a fall. In the records of both these investigations an alkalosis is suggested by the writers as the aetiological factor.

Barker and Sprunt (14) have described a case of tetany which developed as a result of hyperpnoea following encephalitis lethargica. We have been fortunate in observing the following similar case:

TABLE II

(a) Cases of 3 years and under.

Name.	Rickets.	F. P.	Laryng.	Trouss.	K. C. U.	A. C. C.	A. O. C.	K. O. C.	K. C. T.	Alk. Res.	Serum Ca, mg. per 100 c.c.	Serum P, mg. per 100 c.c.
M. B.	+	+	-	-	0.2	0.8	0.4	5.0+	1.6	55.0	4.5	5.8
M. C.	+	+	+	+	0.4	0.4	5.0+	5.0+	1.2	68.1	3.0	5.4
R. R. R.	+	+	-	-	0.8	1.0	1.8	5.0+	2.8	56.5	10.0	8.3
H. McG.	+	+	-	-	0.6	1.2	4.2	5.0+	2.8	53.6	10.5	2.5
M. S.	+	+	-	-	0.8	1.4	2.0	5.0+	2.4	49.7	11.0	4.4
R. L.	+	+	-	-	1.0	1.5	1.5	5.0+	5.0+	53.6	8.4	3.0
M. E.	+	+	-	-	0.8	0.8	2.0	5.0+	2.0	52.6	9.5	4.8
A. Q.	+	+	+	+	0.3	0.8	0.5	5.0+	0.4	44.2	7.5	3.0
J. M.	+	+	+	+	0.6	1.6	1.0	5.0+	1.2	50.7	6.7	3.4
J. D. A.	+	+	-	-	0.9	2.4	1.4	5.0+	1.8	45.8	10.5	3.5
F. D.	+	+	-	-	0.6	2.2	1.2	5.0+	2.2	50.3	8.6	3.2
R. C.	+	+	+	-	0.3	1.3	0.7	5.0+	3.3	7.7	7.7	3.2
F. D.	+	+	+	-	-	-	-	-	-	54.5	6.0	7.3
R. N.	+	+	-	c. p. s.*	0.3	0.6	1.2	0.9	-	52.0	4.8	3.6
J. K.	+	+	convulsions	-	0.3	0.6	0.0	5.0+	1.8	44.9	6.9	6.0
M. F.	+	+	+	+	0.1	0.9	0.7	2.5	-	55.5	5.2	6.8
K. B.	+	+	-	c. p. s.	0.2	1.0	0.7	5.0+	1.5	52.6	8.0	5.0
T. C.	+	+	-	-	-	-	-	-	-	51.0	8.5	3.3
E. D.	+	+	-	-	0.4	2.4	2.5	5.0+	2.2	61.3	10.5	4.3
C. H.	+	+	+	-	0.2	1.1	0.7	3.5	-	51.6	6.6	4.1
M. McA.	-	+	+	-	0.5	1.4	5.0+	5.0+	3.4	53.6	10.5	5.7
J. C.	+	+	-	-	0.6	1.0	1.4	5.0+	2.0	64.2	11.0	3.8
M. C.	+	-	+	-	0.4	1.5	1.5	5.0+	4.0	44.9	7.2	4.0
	+	+	+	-	0.3	0.7	0.9	5.0+	1.8	56.5	8.1	3.3

(b) Cases over 3 years of age.

A. B.	+	+	-	-	0.5	1.3	2.4	5.0+	2.0	50.7	10.2	3.2
R. D.	+	+	-	+	0.5	1.1	1.1	5.0+	2.3	54.5	5.6	1.8
J. McG.	+	+	-	-	0.3	1.2	0.6	5.0+	1.5	57.4	10.5	5.8
A. H.	+	+	-	-	0.8	2.0	1.6	5.0+	2.2	63.2	12.0	5.1
B. K.	+	+	-	-	0.4	1.6	1.4	5.0+	2.0	54.9	10.5	5.2
A. W.	+	+	-	-	0.4	1.0	5.0+	5.0+	1.6	61.3	11.4	5.0
B. J.	+	+	-	-	1.0	1.8	3.2	5.0+	4.0	58.4	10.4	5.7
B. McD.	+	+	-	-	0.7	1.0	5.0+	5.0+	2.2	55.5	10.5	4.0
G. C.	+	+	-	-	0.3	1.1	1.1	5.0+	2.5	53.6	10.5	6.4
P. K.	-	+	-	-	0.6	1.8	1.6	5.0+	4.0	-	11.4	5.1

\* Carpo-pedal spasm.



J. S., aged 5 years, was admitted with marked hyperpnoea which had followed an attack of encephalitis lethargica some months previously. At the height of the hyperpnoea, but after it had existed for about two months, she developed a Chvostek's sign. Her blood calcium was estimated at this time and was found to be 10.3 mg. per cent. (Normal whole blood Ca varies between 7 and 9.)

Also, in the so-called gastric tetany, there is apparently no diminution in the calcium of the serum. Tisdall (15) records two cases in which the serum calcium values were 10.0 and 10.6 mg. per 100 c.c. respectively.

Thus we see that both active and latent tetany may exist without a diminution in the calcium of the serum. In other words, a diminished calcium content of the blood is not an absolutely essential factor in the production of the signs and symptoms of tetany.

*Existence of a Low Calcium Content of the Serum without Signs of Tetany.*

Our attention was first called to the fact that the calcium of the serum may fall to a very low level without resulting in the signs of tetany by the sequence of events in the following case:

*Matthew C.*, aged 13 months, was admitted to hospital on 2.10.23 suffering from gastro-enteritis. He showed evidence of severe rickets. Chvostek's sign was + + + and he had definite laryngismus. On 3.10.23, when seen in the ward after twelve hours' starvation, he had developed an acidosis and all signs of tetany had disappeared. The electrical reactions on this date were:

K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
0.8	1.6	5.0+	5.0+	2.8

The alk. res. was 24.5 vol. %, Ca 3.8 mg. %, and P 7.7 mg. %.

Here then is an instance of a rachitic infant manifesting no symptom of tetany with a serum calcium of only 3.8 mg. per cent.

Also in one other case (F.D., Case VI), recorded in full later, the infant presented no signs of increased mechanical or electrical excitability, although the calcium content of the serum was only 6.1 mg. per cent.

Marriott and Howland (16), and later de Wesselow (17), have reported cases of nephritis in which the serum calcium was greatly diminished (in one of Marriott and Howland's cases as low as 1.5 mg. per cent.), yet no tetany resulted. We have also observed this diminution in nephritis without tetany, as the following case will illustrate:

*Morris J.*, aged 6 years, admitted with acute nephritis and uraemia. During the uraemic stage, the serum phosphorus rose to 8.8 mg. per cent., the serum calcium fell to 4.5 mg. per cent. The CO<sub>2</sub> combining power of the blood-plasma was only 27.4 vol. per cent. No sign or symptom of tetany was present.

Binger (18), by means of intravenous injection of solutions of orthophosphoric acid and its sodium salts in dogs, produced in each case a diminution in the amount of calcium in the serum (from 10.0 mg. per cent. to approximately 6.0 mg. per cent.). Tetany did not result, however, unless the pH of the injected solution was 6.0 or over, and the severity of the tetany depended on

the degree of alkalinity. More recently, Gamble and Ross (19) have recorded the disappearance of the signs of tetany after the administration of  $\text{NH}_4\text{Cl}$ , which caused a relative acidosis, but no rise in the calcium of the serum. We are therefore faced with the fact that a low calcium content of the serum does not necessarily cause signs and symptoms of tetany. Also, where this exists, the disappearance of the symptoms is not necessarily associated with a rise in the calcium.

It must be pointed out that the factor common to all our cases recorded as having a low calcium content without tetany is the existence of a coinciding acidosis. Further, in the cases recorded by others, the existence of an acidosis seemed highly probable from the nature of the disease from which the patients were suffering.

*Effect of Changes in Acid-base Balance on the Signs and Symptoms of Tetany.*

Various salts of calcium have, for many years past, been used for the relief of the symptoms of tetany. It was assumed that their administration supplied the necessary calcium ion. The chloride and the lactate salts have been most extensively used, but it is a known clinical fact that the chloride is the more efficacious of the two. The reason for this was not at first apparent, neither was it explained why these salts were necessary in such large doses.

In 1921 J. B. S. Haldane (20), in studying the effect on metabolism of such salts as calcium chloride and ammonium chloride, showed that they acted by altering the acid-base balance in an acid direction. In the case of calcium chloride, most of the ingested calcium passes through the alimentary tract as an insoluble calcium phosphate, whilst the chlorine ion is absorbed into the blood-stream and combines with a basic radical, thus producing a relative acidosis. In ammonium chloride administration both radicals are absorbed, but the ammonia is rapidly converted into urea, and an effect similar to that of calcium chloride is produced.

Since the present investigation was started, Gamble, Ross, and Tisdall have shown that the beneficial effects of calcium chloride in tetany are not due to the added calcium, but to the relative acidosis which this salt produces. They also showed that the administration of any 'HCl-producing' substance would cause a similar effect, but not necessarily a coincident rise in the calcium value of the serum.

*Administration of Calcium Chloride.*

We quote the following of our cases to illustrate the mode of action of calcium chloride:

*Case I.* Rosetta D., aged 5 years, admitted with late rickets and tetany.

13.12.23. F. P. + + + : Trouseau +.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.5	1.1	1.1	3.5	2.3
	Alk. res. 54.5 vol. %.		Ca 5.6 mg. %.		P 1.8 mg. %.

17.12.23. Had had calcium chloride 2 grm. 4-hourly since last note. F.P. negative: Trousseau negative.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.7	2.8	1.8	—	4.0
	Alk. res. 40.0 vol. %.		Ca 9.5 mg. %.		P 2.8 mg. %.

*Case II.* Matthew C., aged 13 months, moderate rickets present; admitted with gastro-enteritis and tetany.

8.10.23. F.P. + + + : laryngismus + + : Trousseau + +.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.4	0.4	5.0 +	—	1.2
	Alk. res. 68.1 vol. %.		Ca 3.0 mg. %.		P 5.4 mg. %.

9.10.23. Had had six 2 grm. doses of calcium chloride at 4-hourly intervals since last note. F.P. negative: no laryngismus and no Trousseau.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	2.0	1.6	5.0 +	—	5.0
	Alk. res. 40.0 vol. %.		Ca 5.6 mg. %.		P 4.8 mg. %.

11.10.23. Had had no treatment since last note. F.P. still negative: no laryngismus and no Trousseau.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	1.6	1.2	5.0 +	—	3.6
	Alk. res. 41.8 vol. %.		Ca 6.3 mg. %.		P 3.7 mg. %.

13.10.23. F.P. + + + : laryngismus + + : Trousseau + +.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.4	0.2	5.0 +	—	1.8
	Alk. res. 60.3 vol. %.		Ca 3.8 mg. %.		P 5.5 mg. %.

*Case III.* Catherine H., aged 8 months, moderate rickets, admitted with pneumonia and tetany.

15.2.24. F.P. + + + : laryngismus + +.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.2	1.1	0.7	3.5	3.0
	Alk. res. 51.6 vol. %.		Ca 6.6 mg. %.		P 4.1 mg. %.

18.2.24. Had had calcium chloride 2 grm. 4-hourly since last note. F.P. negative: no laryngismus.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	1.2	3.6	1.9	5.0 +	5.0 +
	Alk. res. 36.1 vol. %.		Ca 8.6 mg. %.		P 3.7 mg. %.

21.2.24. Had had no calcium chloride since last note. F.P. + + + : laryngismus + +.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.2	0.6	0.3	3.5	2.5
	Alk. res. 52.5 vol. %.		Ca 6.3 mg. %.		P 3.5 mg. %.

It will be noticed in each case that as the tetany disappeared the calcium content of the serum rose and the alkaline reserve dropped. On stopping treatment, the signs reappeared in from one to three days, the serum calcium fell to its former low level, and the alkaline reserve returned to normal. It will also be observed that the phosphorus content of the serum bore no relationship to the appearance or disappearance of the tetany.

*Administration of Ammonium Chloride.*

This salt was used in a similar manner to note if the mere shifting of the acid-base balance in an acid direction, without the addition of calcium, would accomplish the same result.

*Case IV.* Agnes O., aged 11 months, moderate rickets, admitted as a case of gastro-enteritis.

13.11.23. F. P. + + + : laryngismus + : Trousseau + +.					
E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.3	0.8	0.5	5.0 +	0.4
	Alk. res. 64.2 vol. %.		Ca 7.5 mg. %.		P 3.0 mg. %.
15.11.23. Had had NH <sub>4</sub> Cl 2 grm. 4-hourly since last note. F. P. negative : no laryngismus or Trousseau.					
E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.8	2.4	3.6	5.0 +	3.0
	Alk. res. 41.0 vol. %.		Ca 9.9 mg. %.		P 2.8 mg. %.

*Case V.* Jessie M., aged 12 months, moderate rickets, admitted with tetany and a history of convulsions.

17.11.23. F. P. + + + : Trousseau +.					
E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.6	1.6	1.0	5.0 +	1.2
	Alk. res. 50.7 vol. %.		Ca 6.7 mg. %.		P 3.4 mg. %.
18.11.23. Had had six 2 grm. doses of $\text{NH}_4\text{Cl}$ at 4-hourly intervals since last note. F. P. negative: no laryngismus or Trousseau.					
E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	1.3	3.8	5.0 +	—	4.8
	Alk. res. 42.9 vol. %.		Ca 8.0 mg. %.		P 2.5 mg. %.

*Case VI.* Frances D., aged 9 months, moderate rickets, admitted with tetany.

2.12.23. F. P. + + + : laryngismus + : E. R. not done.					
Alk. res. 54.5 vol. %.		Ca 6.0 mg. %.		P 7.3 mg. %.	
4.12.23. Had had ten 2 grm. doses of $\text{NH}_4\text{Cl}$ at 4-hourly intervals since last note. F. P. negative : no laryngismus.					
E. R. :	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	1.0	2.3	1.7	—	4.5
Alk. res. 47.7 vol. %.		Ca 6.1 mg. %.		P 5.3 mg. %.	

In Cases IV and V the tetany disappeared and the serum Ca rose coincident with the fall in the  $\text{CO}_2$  combining power to 41.0 and 42.9 vol. per cent. respectively. Case VI is of special interest because the tetany disappeared although the calcium of the serum remained unaltered. This might be accounted for by the fact that the alkaline reserve fell only to 47.7 vol. per cent. On the other hand, Gamble, Ross, and Tisdall, in some of their cases, observed a much more striking fall in the alkaline reserve than we have ever obtained, but without any resultant rise in the blood Ca. They suggest that in these cases an increase in the ionized Ca is responsible for the beneficial effect produced.

*Pathological Acidosis.*

We have been fortunate during the past year in observing the development of pathological acidosis in three cases suffering from tetany. These cases are as follows:

*Case VII.* Malcolm E., aged 17 months: moderate rickets.

10.11.23. Admitted with gastro-enteritis. F.P. + + +: history of recent carpo-pedal spasm: no laryngismus or Trousseau demonstrable.

11.11.23. As the result of a 12-hour starvation period, patient had developed an acidosis. F.P. negative: no laryngismus or Trousseau.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.8	2.8	5.0+	5.0+	4.4
	Alk. res. 35.2 vol. %.		Ca 8.5 mg. %.		P 4.4 mg. %.

14.11.23. Had been getting  $\text{NaHCO}_3$  2 grm. 4-hourly since last note. F.P. + + +: no laryngismus or Trousseau.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.3	0.8	2.0	—	1.6
	Alk. res. 50.7 vol. %.		Ca 9.4 mg. %.		P 4.7 mg. %.

*Case VIII.* Matthew C., aged 13 months, markedly rachitic infant.

2.10.23. Admitted with gastro-enteritis. F.P. + + +: laryngismus +: no Trousseau.

3.10.23. Following a 12-hour starvation period, patient developed acidosis. All signs of tetany had disappeared.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.8	1.6	5.0+	—	2.8
	Alk. res. 34.5 vol. %.		Ca 3.8 mg. %.		P 7.7 mg. %.

5.10.23. Had had  $\text{NaHCO}_3$  2 grm. 4-hourly since last note. F.P. +: no laryngismus or Trousseau.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.6	2.0	5.0+	—	2.8
	Alk. res. 47.7 vol. %.		Ca 4.1 mg. %.		P 5.4 mg. %.

8.10.23.  $\text{NaHCO}_3$  treatment continued. F.P. + + +: laryngismus + +: Trousseau + +.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.4	0.4	3.0	—	1.2
	Alk. res. 68.1 vol. %.		Ca 3.0 mg. %.		P 5.4 mg. %.

*Case IX.* Ronaldo C., aged 22 months, markedly rachitic infant.

14.12.23. Admitted with rickets and tetany. F.P. + + +: laryngismus +.

15.2.23. Developed acidosis overnight, cause unknown. All signs of tetany had disappeared.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.7	2.0	2.0	—	2.5
	Alk. res. 38.1 vol. %.		Ca 9.5 mg. %.		P 3.3 mg. %.

18.2.23. Had been on  $\text{NaHCO}_3$  2 grm. 4-hourly since last note. F.P. + + +: laryngismus +: Trousseau negative.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.3	1.3	0.7	—	3.3
	Alk. res. 54.5 vol. %.		Ca 7.7 mg. %.		P 3.2 mg. %.

These observations are of special interest in view of the fact that they show the importance of pathological changes in the acid-base balance in determining the existence or non-existence of the signs of tetany. Especially in Case VIII does this appear to be the case. Although all signs of tetany had disappeared coincident with the existence of a low alkaline reserve, the calcium content of the serum was only 3.8 mg. per cent. In each case on restoring the alkaline reserve to normal by the administration of  $\text{NaHCO}_3$  the signs of tetany again became manifest.

The  $\text{NaHCO}_3$  appears to produce its effect merely by hastening the disappearance of the existing acidosis which had masked the presence of tetany.

Howland and Marriott (8), in their communication on infantile tetany published in 1918, make the following statement: 'After therapeutic administration of bicarbonate of soda for acidosis it is not unusual to see the development of characteristic symptoms of tetany. Thus, we have seen typical carpo-pedal spasm when bicarbonate of soda has been injected intravenously for the *acidosis*<sup>1</sup> of diarrhoea.' They quote three cases in support of this statement.

In view of our observations that no signs or symptoms of tetany can be elicited during the existence of an acidosis, it would be necessary, before believing that the alkali induced the tetany, to know whether or not the children quoted by the above authors had signs of tetany prior to the onset of the acidosis. Unfortunately from their published protocols it is impossible to ascertain this. In one of the cases an acidosis was admittedly present on admission, whilst the other two were suffering from diseases in which an acidosis is extremely liable to occur. The possibility, therefore, arises that the administration of the bicarbonate of soda caused a pre-existing tetany to reappear as the acidosis cleared up.

Indeed, we have seen tetany appear in a child convalescing from an acidosis without the administration of any sodium bicarbonate. The following case will illustrate this:

*Case X.* Agnes A., aged 11 months, a rachitic infant, was admitted to hospital on 3.11.23 with gastro-enteritis and acidosis. The facial phenomenon was negative. There had been no convulsions and there was nothing in the history to call attention to the possible existence of tetany. However, as the acidosis cleared up with the cessation of the diarrhoea, signs of tetany manifested themselves. On 13.11.23 the F.P. was + + +; laryngismus was present, and Trousseau's sign was elicited.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	0.3	0.8	0.5	—	0.4
	Alk. res. 64.2 vol. %.		Ca 7.5 mg. %.		P 3.0 mg. %.

No alkali of any kind had been administered to this infant during the period of observation. We believe that she was suffering from latent tetany before the onset of the gastro-enteritis.

Attention may also be called to the well-known fact that following con-

<sup>1</sup> The italics are ours.



vulsive seizures in a child with tetany, the facial phenomenon is frequently absent. It seems not improbable that the disappearance of this sign may be accounted for by the existence of a transient acidosis resulting from the convulsions.

*The Relationship of Tetany to Alkalosis.*

It is evident from the results quoted above that an acidosis, no matter how produced, invariably leads to the disappearance of the signs of tetany, and this apparently irrespective of the total calcium content of the serum. Is the hyper-excitability of the nervous system, then, the result of an alkalosis?

Such a possibility has been considered, and evidence in support of this view has been supplied by Wilson and his fellow-workers (21), who describe an alkalosis in parathyroid tetany in dogs. Furthermore, as already indicated, Binger (18) produced a reduction of the calcium content of the blood by means of both acid and alkaline phosphates, but only when the alkaline phosphate solutions were injected was the calcium fall accompanied by tetany.

Morris (22), in animals, studied the cause of the increased electrical excitability manifested by the neuro-muscular system. He concluded that the administration of alkalis, by producing an alkalosis and lowering the oxygen supply of the tissues, caused an increase in the electrical excitability, but Henderson (23), who gave large doses of sodium bicarbonate by mouth to children, did not find any increase in the electrical excitability.

Gastric tetany, we know, is accompanied by a very marked rise in the alkaline reserve, and hyperpnoeic tetany has invariably been put down to an alkalosis.

We have attempted on many occasions to produce an alkalosis by means of oral administration of alkali. In only three cases did we succeed in raising the alkali reserve appreciably above normal, but in no case did tetany result.

The following are brief abstracts of the cases in point:

*Case XI.* Duncan C., aged 5 years—admitted on 13.11.23 with severe acidosis as a result of ileo-colitis. No clinical evidence of rickets. No signs or history of tetany. He was given  $\text{NaHCO}_3$ , grm. 2, every 2 hours for the first 24 hours, after which the dose was reduced to grm. 2, four times daily.

On 17.11.23 there was no sign of tetany.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	1.0	1.0	5.0+	5.0+	4.8
	Alk. res. 91.8 vol. %.		Ca 10.4 mg. %.		P 4.1 mg. %.

*Case XII.* David L., aged 6 years, with no evidence of rickets or tetany, was admitted on 11.11.23 with dysentery and acidosis. He was given  $\text{NaHCO}_3$ , grm. 2, 4-hourly.

17.11.23 no signs of tetany.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	1.90	1.2	5.0+	—	4.8
	Alk. res. 82.6 vol. %.		Ca 9.5 mg. %.		P 4.4 mg. %.

*Case XIII.* Dora McL., aged 7 years, admitted with pyelitis and acidosis on 23.10.23. Was given  $\text{NaHCO}_3$ , 1.5 grm., 8 times daily.

On 9.11.23 there were no signs of tetany.

E. R.:	K. C. C.	A. C. C.	A. O. C.	K. O. C.	K. C. T.
	1.6	2.6	2.4	—	5.0+
	Alk. res. 73.9 vol. %.		Ca 10.2 mg. %.		P 5.4 mg. %.

It will be observed that the 3 cases in which we found an increase in the alkaline reserve were all children in whom a disturbance of the acid-base balance had previously existed. No signs of tetany resulted from the alkalosis produced, nor was the calcium content of the serum diminished (9.5 in Case XII may be considered normal when the experimental error is allowed for). We have never succeeded in raising the alkaline reserve above normal in a healthy infant by oral administration of sodium bicarbonate, although we have repeatedly tried to do so.

It may also be mentioned that continued administration of  $\text{NaHCO}_3$  failed to produce any increase in the severity of the symptoms after these had manifested themselves. Hence we must conclude that alkalosis, as far as this can be demonstrated by the Van Slyke method, is not the essential factor in the production of the signs and symptoms of tetany.

#### *Summary and Discussion.*

It is evident from the foregoing results that, from blood examination in untreated cases, we have not been able to find a single feature which is common to all children with idiopathic tetany.

Regarding the phosphorus content of the serum, our figures explain themselves. No relationship can be shown to exist between the level of the serum phosphorus and the symptoms of tetany. Elias and Spiegel (24) believe that 'hyperphosphæmia' is one of the factors in the production of tetany.<sup>2</sup> Binger's

<sup>2</sup> Since this paper was sent to the press Salvesen (*Acta Medica Scandinavica*, Supplementum VI, 1923) emphasizes the importance of the calcium reduction as an aetiological factor in the production of the symptoms of parathyroid tetany in dogs, and suggests that this reduction may be brought about by abnormally increased excretion of calcium by the bowel. This theory is apparently largely based on the fact that when calcium was injected intravenously in sufficient quantity to raise the blood calcium considerably above the normal figure, 80 per cent. to 90 per cent. of the injected calcium was excreted by the bowel. It is however extremely doubtful whether this excessive excretion can occur unless under such abnormal conditions as that produced by the introduction into the blood-stream of a large quantity of calcium in the form of a salt not normally present in the blood. There is no evidence in support of the view that excretion by the bowel takes place when the blood calcium is normal or slightly reduced, as it presumably is in the infant before the onset of tetany.

Salvesen further suggests that the increased phosphate content of the blood, which he was able to demonstrate in all cases after parathyroidectomy, may be the cause of the increased calcium excretion, and quotes the work of Binger (18) in support of such a theory. While we are familiar with the fact that parathyroid tetany is accompanied by a rise in the blood phosphorus, our figures show that the phosphorus level in idiopathic tetany bears no relationship to the presence or absence of the symptoms. It is difficult to make a high phosphate theory of calcium reduction fit in with our knowledge of conditions leading to the onset of infantile tetany when we remember that this most commonly occurs in the rachitic

experiments indicate that it is the reaction of, rather than the amount of, phosphorus in the solution injected which determines whether tetany appears or not. In nephritis, where the blood phosphates frequently reach a high level, tetany does not result.

The experimental and clinical evidence in favour of the calcium deficiency theory seems, at first glance, overwhelming. However, there is equally strong evidence against it, unless we are to explain some of the results by admitting that the same condition may arise from various different causes. That calcium reduction was an accompaniment of all our cases of active tetany we do not deny, but a cure of the condition does not necessarily result in a rise in the serum calcium level. Neither can we show that the severity of the symptoms varies in proportion to the diminution of the calcium. Reference to Table II shows that A. Q., with active tetany, had a serum calcium content of 7.5 mg. per cent., while M. B., with an F.P. ++ but no other sign of tetany, had a calcium value of 4.5 mg. per cent. Also, K. B., with severe carpo-pedal spasm, had a serum Ca value of 8.0 mg. per cent., which is almost as high as that of R. L., who had neither carpal spasm nor marked increase in electrical excitability.

Gamble and Ross (19) have advanced the theory that the proportion of 'ionized calcium' is the important factor in determining the onset of the symptoms. On the basis of such a theory one might be able to explain the non-existence of tetany in the presence of a low total Ca by assuming that all or most of this element is ionized as a result of the coexisting acidosis. It may, however, be mentioned that we have recorded a serum Ca value of 3.8 mg. per cent. (M. C., Case VIII) and Marriott and Howland (16) have recorded a value as low as 1.5 mg. per cent. without the appearance of signs of tetany. It is evident that even were all of the available calcium in the serum ionized in these two cases there would still be a deficiency of calcium ions, since Rona and Takahashi (25) have shown that one-third of the total, or approximately 3.5 mg. per cent., is the normal amount. We have not had an opportunity of investigating possible changes in the ionized Ca in tetany, and are not therefore in a position to discuss the aetiology from this point of view.

From time to time, various workers have suggested that increase in the sodium or potassium of the blood might give rise to tetany. Salts of these two elements have been known since the time of Loeb to act as irritants on the nervous system, while calcium and magnesium are sedatives. Though it is clear that a diminution in the calcium will cause a disturbance of the ratio of irritant to sedative salts, it has never been definitely proved that increase in sodium or potassium in the blood in the presence of a normal calcium is responsible for increased electrical irritability. We have estimated the sodium and potassium in 3 cases of latent tetany which showed normal serum-calcium values. In each case the figures obtained were within the normal limits. No disturbance of the salt ratio could therefore be demonstrated.

In our experience the production of an acidosis always causes the signs of tetany to disappear. This fact and the experimental work cited above certainly suggest that the symptoms result from an alkalosis. But if such be the explanation it is quite apparent from our results that this alkalosis is not measurable by means of the Van Slyke method.

It is further admitted that, even if it can be proved that alkalosis is the factor of importance in the production of the symptoms, we are still no nearer the discovery of the actual cause of the disease. We do not yet know of any pathological condition in childhood which will give rise to an alkalosis, though it is well recognized that acidosis is readily produced.

The possibility that some toxin may produce an 'alkalotic' effect must of

infant in whom the blood phosphorus has been below the normal level for some considerable time and in whom the blood calcium is normal.

course be considered, and the effect on the acid-base balance of injections of guanidine seems worthy of investigation.<sup>3</sup>

At the present time one cannot make any further suggestion than that the causative factor, whatever this may be, is incapable of producing its effect in the presence of an acidosis, but that any shift of the acid-base balance in an alkaline direction tends to favour its harmful effect.

#### Conclusions.

1. Active tetany is always accompanied by a diminished calcium content of the serum. The severity of the tetany, however, bears no relation to the diminution of the calcium.

2. Latent tetany may or may not be accompanied by a low calcium content of the serum.

3. The production of acidosis invariably leads to the disappearance of the signs of tetany, irrespective of a rise in the calcium content of the serum.

4. The  $\text{CO}_2$  combining power of the venous plasma is within normal limits in infantile tetany.

We have pleasure in acknowledging our indebtedness to Dr. Leonard Findlay and Professor D. Noel Paton for much helpful advice and kindly criticism.

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#### REFERENCES.

1. Sabatini, 'Funzione biologica del Calcio', *Accad. Reale delle Scienze di Torino*, 1904.
2. Quest, *Jahrb. f. Kinderh.*, Berlin, 1905, lxi. 114.
3. MacCallum and Voegtlin, *Journ. Exper. Med.*, New York, 1909, xi. 118.
4. MacCallum, Lambert, and Vogel, *ibid.*, New York, 1914, xx. 149.
5. Cattaneo, *La Pediatria*, Napoli, 1909, 2nd series, vii. 414.
6. Longo, *Policlinico*, Roma, 1910, xvii, Sez. Med., 495.
7. Neurath, *Zeitsch. f. Kinderheilk.*, Berlin, 1910, i. 1-42.
8. Howland and Marriott, *Quart. Journ. Med.*, Oxford, 1917-18, xi. 289.
9. Kramer and Tisdall, *Journ. Biol. Chem.*, Baltimore, 1921, xlviii. 223.
10. Tisdall, *ibid.*, Baltimore, 1922, i. 329.
11. Van Slyke, *ibid.*, Baltimore, 1917, xxx. 347.
12. Collip and Backus, *Amer. Journ. Physiol.*, 1920, li. 568.
13. Grant and Goldman, *ibid.*, 1920, lii. 209.
14. Barker and Sprunt, *Endocrinology*, Glendale, California, 1922, vi. 1-14.
15. Tisdall, *Journ. Biol. Chem.*, Baltimore, 1922, liv. 35.
16. Marriott and Howland, *Arch. Int. Med.*, Chicago, 1916, xviii. 708.
17. de Wesselow, *Quart. Journ. Med.*, Oxford, 1922-3, xvi. 341.
18. Binger, *Journ. Pharmacol. & Exper. Therap.*, Baltimore, 1917-18, x. 105.
19. Gamble and Ross, *Amer. Journ. Dis. Child.*, Chicago, 1923, xxv. 470.
20. Haldane, *Journ. Physiol.*, Camb., 1921, lv. 265.
21. Wilson, Stearns, and Thurlow, *Journ. Biol. Chem.*, Baltimore, 1915, xxiii. 89.
22. Morris, *Brit. Journ. Exper. Path.*, 1922, iii. 101.
23. Henderson, *Quart. Journ. Med.*, Oxford, 1919-20, xiii. 427.
24. Elias and Spiegel, *Wien. Arch. für inn. Med.*, 1921, ii. 447.
25. Rona and Takahashi, *Biochem. Zeitsch.*, Berlin, 1913, xlix. 370.

<sup>3</sup> Salvesen in the study quoted on p. 74 investigated the effect of guanidine injections in the dog. His results, however, can hardly be regarded as conclusive, since his observations were limited to three experiments on one animal. In the first two experiments no tetany was produced by the dose of guanidine used, and in the third the alkaline reserve is not recorded.

## ON THE PATHOLOGY OF NEPHRITIS ASSOCIATED WITH OEDEMA, AS ILLUSTRATED BY SIX CASES

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With Plates 1-3

IN a previous communication (1) the present author described the macroscopic and microscopic appearances presented by the kidneys after death, and the results of certain biochemical tests performed during life in a number of cases of nephritis of the 'primary chronic interstitial type'. Clinically, these were all characterized by an insidious onset, progressive increase in blood-pressure, polyuria, albuminuria of a moderate degree, the presence of little or no oedema, and a termination in 'uraemia'. The biochemical tests showed a slow but steady increase in the percentage of urea in the blood, together with an increasing inability to excrete this substance when taken by the mouth. Histologically, the kidneys all agreed in showing cuneiform areas of fibrosis, with hypertrophy of the intervening tissue, degenerative and inflammatory changes of the glomeruli, and that peculiar hyperplasia accompanied by fatty change of the arterioles first described by Jores (2), and more recently fully considered in this country by Evans (3), under the name of 'diffuse hyperplastic sclerosis'.

The history and course of the condition, the biochemical findings during life, and the histological appearances of the kidney after death all serve to mark this condition as a very definite pathological entity, and as such it was described by Gull and Sutton (4) in their classical paper on the subject. The subject is rendered difficult by the fact that, as has been pointed out by MacLean (5) and others, an identical clinical picture may arise as the result of changes occurring in the kidney following upon an attack of 'acute nephritis'. This has led Shaw Dunn (6) to postulate an unnoticed condition of acute inflammation as the necessary precursor of every case of 'primary chronic interstitial nephritis'. The subject-matter of the present communication consists of a series of six cases of nephritis of the type usually known as 'chronic parenchymatous', all more or less acute in their onset. They are presented with the view of considering, among other points, whether, had death not supervened when it did, they would later have conformed to the 'chronic interstitial' type.



Clinically, the one feature common to all the cases to be described was oedema. In every case this was extreme in degree, and even by itself served to remove the condition at once from the category of 'interstitial' nephritis as the term is customarily employed. Histologically, the one common feature was the presence of very marked degeneration of the tubular epithelium, accompanied in every instance by the deposition, in most cases to a very striking degree, of doubly refracting material giving the staining reaction of fat. This tubular change was not by any means the only abnormal histological finding; glomerular changes were also present in every case and served, in some sort, in conjunction with the clinical findings, to divide the cases into two groups. In the first group fall those cases in which oedema and albuminuria alone were the outstanding clinical features; histologically, the kidneys from these cases showed no evidence of inflammation of, but a greater or less degree of degenerative change of, the glomeruli, as evidenced by loss of differentiation of the loops of the tuft, increase or disappearance of the nuclei, and alterations in their staining properties, all the glomeruli being in the same state. In the second group, in addition to oedema and albuminuria, macroscopic haematuria was present. Histologically, the kidneys from these cases, in addition to the common tubular changes described above, showed gross alteration of the glomeruli; in two of the cases the glomerular changes were definitely inflammatory, in the remaining one due to 'amyloid' change, but in every instance there was gross alteration in the glomerular morphology. All the cases in this group showed a progressive tendency towards a failure to excrete urea and a slow but progressive rise in blood-pressure.

*Features Common to all Cases.*

*Clinical.* Oedema, albuminuria, cylindruria.

*Histological.* Degeneration of epithelium of renal tubules. Deposition in degenerated renal tubular epithelium of large quantities of doubly refracting fatty material.

Group A. Cases 103, 130, 133.

*Common clinical features.* Oedema, albuminuria; no urea retention; no rise in blood-pressure.

*Common histological features.* Degeneration of renal tubular epithelium; deposition of doubly refracting fatty substances; more or less degenerative change of the glomeruli. Little or no interstitial inflammation.

Group B.

*Common clinical features.* Oedema, albuminuria, haematuria; tendency towards urea retention and slow but progressive increase in blood-pressure.

*Common histological features.* Degeneration of renal epithelium and deposition of doubly refracting fatty material as in Group A.



## Sub-group 1. Cases 94 and 111.

Proliferation of glomerular endothelium, adhesions between tufts and capsule, and other signs of inflammation. Glomeruli showing various stages of the inflammatory process. Evidence of intense interstitial inflammation.

## Sub-group 2. Case 125.

'Amyloid' change of glomerular tuft.

## GROUP A.

*Case 103.* Male. Aged 8. Only previous illness scarlet fever at age of 3, and was then not ill long. One week before admission the mother noticed that the patient's face was swollen; later the swelling extended to the feet. Appetite remained good, and there was no complaint of pain, headache, or malaise. On admission, August 15, 1922, patient was pale; there was marked general oedema. Pulse and respiration normal. Urine contained much albumin, but no blood; granular casts were present in fair numbers. Blood-pressure, 83/52.

On August 30 the patient was put on a daily dose of 45 gm. of urea by mouth. This was followed by a slight increase in the daily output of urine, but by no marked change in the degree of the oedema. On September 19 the daily dosage of urea was raised to 77 gm., at which level it was maintained until death. The oedema and general condition of the patient remained practically unaltered from the date of admission until October 11, when the temperature suddenly rose to 103°. Death occurred the following day.

The result of the biochemical tests in this case were as follows:

August 19. Blood urea, 31 mg. per cent.

Urea concentration in urine, 3.2 per cent.

August 30. Blood urea, 22 mg. per cent.

Urea concentration in urine after 15 gm. urea by mouth:

1st hour, 4.5 per cent. in 90 c.c.

2nd hour, 3.5 per cent. in 93 c.c.

3rd hour, 3.5 per cent. in 93 c.c.

September 16. Blood urea, 35 mg. per cent.

Urea concentration in urine, 3.85 per cent.

It is to be noted that between this last test and the preceding one urea medication by the mouth had been commenced.

The blood-pressure readings in this case were: on admission, 83/52; September 9, 93/65; September 18, 80/58; October 6, 100/70.

The Wassermann reaction was negative.

*Post mortem* it was evident that the sudden and unexpected death had occurred as the result of a low-grade infection in the peritoneal cavity. The whole body was very oedematous; there was marked ascites, the ascitic fluid being milky and containing flakes of lymph; the peritoneum was slightly injected; a thorough search failed to reveal any focus in which the peritoneal infection might have originated. The kidneys were large and pale, each weighing 4½ oz. The capsule stripped readily, leaving a smooth surface; on section the cortex was swollen and light yellow in colour. The heart appeared normal, weighing 3½ oz. Much free fluid was present in the pleural and pericardial sacs.

*Histology.* Beyond a certain amount of oedema the interstitial substance of this kidney showed no change whatever; there was no fibrosis and no suspicion of round cells. A little fat was present in the interstitial substance, some of it anisotropic.

The most striking change from the normal was in the tubules, of which the epithelium showed evidence of severe damage. In paraffin sections the cyto-

plasm of the damaged cells presented an opaque homogeneous appearance; many had lost their nuclei; the nuclei of many others failed to take the stain in a normal manner. The free edges of the cells were irregular and broken. Many of the tubules contained casts. In suitably stained frozen sections the damaged epithelial cells were seen to be loaded with fat; this applied more particularly to those of the convoluted tubules, but those of the collecting tubules and of the ascending limb of Henle's loop were similarly affected, although to a lesser degree. Most of this fat stained dark blue with Nile blue sulphate, which would point to its being fatty acid rather than neutral fat. Examination under the crossed Nicol prisms showed that many of the droplets in the epithelial cells were doubly refracting.

The changes in the glomeruli were not at first glance so striking as those in the tubules. Very definite evidence of a morbid process affecting all the glomeruli was, however, supplied by the appearance of the tufts (Fig. 1, Plate 1). These showed swelling of the endothelium and an apparent increase in the number of nuclei present. Less definite pathological appearances were general swelling of the tufts and loss of differentiation between the individual loops. All the glomeruli were in the same condition.

The vessels showed no change from the normal.

*Case 130.* Male. Aged 56. Diphtheria and typhoid fever forty years previously; otherwise no illness up to 1915. From that time onwards the patient stated that he suffered from occasional attacks of swelling of the feet, but the history on this point was very indefinite. In 1920, during one of these attacks, apparently somewhat more severe than those that had preceded it, patient consulted a doctor, who found his urine to contain albumin. Patient stayed away from his work for one month and returned feeling quite well, though still with slight swelling of the feet. The swelling grew worse, and eighteen months before admission to hospital he was forced to give up his work, to which he never returned. On admission, June 5, 1923, the patient showed marked oedema of the legs, and to a lesser degree of the arms. He was pale and the face was puffy; he made no complaint of pain or headache; appetite good; blood-pressure, 170/100; urine, much albumin; no blood or pus; few hyaline casts.

The course of the case was steadily downhill from the time of admission; the appetite became poor; headaches appeared and increased in severity; towards the end there was vomiting and pain in the left leg, for which no cause could be found. Death occurred 28.9.23.

The results of the biochemical tests in this case were as follows:

- May 6. Blood urea, 29 mg.  
Urea concentration in urine, 1.18 mg. per cent.  
After 15 gm. urea by mouth:
  - 1st hour, 1.15 per cent.
  - 2nd hour, 1.16 per cent.
  - 3rd hour, 1.46 per cent.Urea concentration factor, 1/48.
- May 28. Blood urea, 54 mg. per cent.
- Aug. 13. Blood urea, 35 mg. per cent.  
Urea in urine, 1.5 per cent.  
Urea in urine after 15 gm. urea by mouth:
  - 1st hour, 1.75 per cent.
  - 2nd hour, 2.1 per cent.
  - 3rd hour, 2.3 per cent.Urea concentration factor, 1/50.

*Post mortem.* The body showed an intense generalized oedema; all serous sacs contained large quantities of clear fluid. Lungs normal, except for oedema; heart, weight 12 oz., not enlarged; kidneys, weight 9½ and 10 oz., large, pale,

capsule not thickened and stripped readily, leaving a smooth surface; on section the cortex was not reduced; in colour it was pale yellow. Liver somewhat cirrhotic and very fatty; spleen large and of firm consistency.

*Histology.* The framework of the kidneys showed a general diffuse fibrosis, almost unaccompanied by round-celled infiltration or other signs of inflammation. The tubules showed degeneration of the epithelium and the presence of a very large amount of fat, all of which appeared to be doubly refracting (Fig. 2), both within the degenerating epithelial cells and also in the lumina. The glomeruli (Fig. 3) were universally affected and almost all to the same degree; the morbid change consisted in a very intense degree of hyaline degeneration of the tufts; round-celled infiltration, endothelial proliferation, and other signs of inflammation were entirely absent, and the capsules showed little or no thickening; in every case, however, the tufts showed loss of differentiation of the loops, and diminution in the number of the nuclei. In the most extreme examples the whole tuft was represented merely by a homogeneous disk showing a few degenerate nuclei. In all cases the degenerated tuft was so swollen as to fill the capsular space, and in some cases to protrude into the efferent tubule. Beyond some hyaline change of the media and some splitting of the internal elastic lamina of the arterioles, the vessels showed no morbid change. In some sections the very large amount of anisotropic fat-staining substance present was a striking feature. This, as already mentioned, was most plentiful in the degenerated epithelium of the convoluted tubules; it was absent from the interstitial tissue.

*Case 133.* Female. Aged 48. Married, three children, all healthy. First noticed swelling of the feet in July 1923, admitted August 3, 1923. Patient then showed ascites and much oedema of the legs and feet; her urine contained albumin in large quantities, but no blood. Patient was treated by rest in bed and a salt-free diet; her teeth, which were very septic, were all extracted. She was discharged free from oedema and ascites on September 4. A week later she was readmitted in very much the same condition as on first admission. She was again treated by salt-free diet, and also for a time by urea by the mouth. On October 18,  $7\frac{1}{2}$  pints of fluid were removed by paracentesis from the peritoneal cavity; on November 28,  $13\frac{1}{2}$  pints were similarly removed. On December 6 patient suffered from sore throat, accompanied by swelling of the glands of the neck and of the left arm and hand; this condition improved, but a week later patient complained of abdominal pain; the pain was not severe, and there was no rigidity or other sign of abdominal trouble. None the less, death occurred on December 15.

The results of biochemical tests in this case were as follows:

August 9. Blood urea, 29 mg. per cent.

Urine urea, 1.8 per cent.

Urea concentration factor,  $1/72$ .

Urea concentration in urine after 15 gm. urea by mouth:

1st hour, 1.74 per cent.

2nd hour, 1.98 per cent.

3rd hour, 2.09 per cent.

September 27. Blood urea, 29 mg. per cent.

Urine urea, 2 per cent.

Urea concentration factor,  $1/68$ .

Urine urea concentration after 15 gm. urea by mouth:

1st hour, 2 per cent.

2nd hour, 2.3 per cent.

3rd hour, 3.5 per cent.

October 12. Blood urea, 136 mg. per cent. (Patient had been receiving from 20 to 60 gm. of urea daily by mouth; this was now stopped.)

October 15. Blood urea, 36 mg. per cent.

November 8. Blood urea, 127 mg. per cent.

*Blood-pressure.* August 13, 125/155; October 18, 93/125; December 3, 90/130.

*Post mortem.* It was evident that in this case the cause of death had been a low-grade peritonitis. Fluid was present in all the serous sacs, but that in the peritoneal cavity was slightly turbid, and contained flakes of lymph. No focus of infection was present. The heart showed some petechial spots upon the epicardium, and a few similar spots were present on the visceral pleura. The heart was small, weighing  $7\frac{1}{2}$  oz. The kidneys were of slightly more than normal size, weights 6 and 7 oz. The capsule was not thickened, and stripped readily, leaving a very finely granular surface; on section the cortex was of normal depth, and pale and greasy in appearance; the medulla was congested.

*Histology.* The framework showed a slight degree of fibrosis; this was generalized, its distribution wanting the wedge-shaped arrangement characteristic of 'chronic interstitial' nephritis. Doubly refractive fatty material, contained within phagocytic cells, was present in fair quantities in the fibrous tissue of the framework. The tubular system showed cloudy swelling of the epithelium throughout; the epithelium of the convoluted tubules and of the ascending limb of Henle's loop showed intense 'fatty' change; examination under the crossed Nicol prism revealed the fact that all this 'fat' was doubly refractive; in some of the convoluted tubules the epithelium was completely replaced by crystalline masses of this anisotropic fat-like substance. The glomeruli were universally affected, and all in the same stage of morbid process. The principal changes were loss of differentiation of the loops of the tuft (Fig. 4), and an apparent increase, with degeneration, of the nuclei. None of the glomeruli showed any round-celled infiltration or other signs of inflammation. The vessels showed no change from the normal.

## GROUP B.

### *Sub-group 1.*

*Case 94.* Male. Aged 27. Only previous illness malaria in 1916. Two months before admission to hospital, while feeling in normal health, noticed that his urine was dark red in colour; this continued on and off until admission. During the last two weeks before admission there was swelling of the face and feet. On admission to hospital, October 22, 1921, there was marked general oedema, and blood and albumin were present in the urine in large amounts. The patient made no complaint of pain, headache, or any discomfort.

In January 1922 the patient first complained of headache, and at times was drowsy. At first both these symptoms only occurred intermittently, but as time went by the frequency of the attacks increased, and by March 1922 they were almost continuous. Oedema of the optic disks was now noted. In April 1922 convulsive seizures of 'uraemic' type first made their appearance; these continued at varying intervals and with varying frequency until death. Throughout this time the oedema, except for slight fluctuations, showed a steady increase. Death occurred in coma on July 17, 1922.

The results of the biochemical tests for renal function in this case were as follows:

November 21, 1921.	Blood urea, 47 mg. per cent.
" 29, "	Blood urea, 46 mg. per cent.
" 30, "	Urea concentration in urine after 15 grm. by mouth:
	1st hour, 1.37 per cent. in 112 c.c. urine.
	2nd hour, 1.54 per cent. in 64 c.c. urine.
	3rd hour, 1.6 per cent. in 71 c.c. urine.

## PATHOLOGY OF NEPHRITIS ASSOCIATED WITH OEDEMA 83

January 17, 1922. Urea concentration after 15 grm. by mouth :  
1st hour, 1.55 per cent. in 67 c.c.  
2nd hour, 1.59 per cent. in 34 c.c.  
3rd hour, 1.39 per cent. in 45 c.c.

March 1, 1922. Blood urea, 48 mg. per cent.  
After 15 grm. urea by mouth, blood urea, 90 mg.  
Urea concentration in urine:  
1st hour, 0.9 per cent. in 170 c.c.  
3rd hour, 1.0 per cent. in 35 c.c.

On the basis of these last results Professor MacLean reported: 'The amount of actual kidney tissue left is hardly sufficient to carry on normal function; destruction of renal tissue appears to be steadily progressive, as indicated by tests and the very large number of casts present.'

April 12, 1922. Blood urea, 152 mg. per cent.

" 21, " Blood urea, 330 mg. per cent.

May 26, " Blood urea, 261 mg. per cent.

Except when noted, the patient received no urea by mouth.

The blood-pressure showed a progressive rise; in January it was 135/100; in March, when the last reading was taken, 190/110.

*Post-mortem.* The kidneys were normal in size; the capsule stripped readily, leaving a smooth surface. The heart showed hypertrophy of the left ventricle and was definitely enlarged; weight, 17½ oz. All the organs were oedematous, and much fluid was present in the pleural, peritoneal, and pericardial sacs.

*Histology.* The framework of the kidney showed a very considerable increase in fibrous tissue. This fibrosis was diffuse and universal throughout the organ, there being no indication of the wedge-shaped distribution seen in the kidneys of the diffuse hyperplastic sclerotic type. Throughout the newly formed fibrous tissue was a diffuse infiltration by round cells of the lymphocyte class; of these cells there were some small local collections, but this infiltration was nowhere very dense.

The changes in the glomeruli were the most striking feature (Fig. 5, Plate 2): no normal glomeruli were present; all showed some pathological condition, and of this condition various stages were present. Some showed hypertrophy of the tuft, with increase in nuclei and proliferation of the capsular endothelium; in these, well-formed endothelial crescents were often present, and many showed adhesions between capsule and tuft. In a later stage of the morbid process the tuft showed hyaline change, and in some cases droplets of fat were present; the final stage was fibrosis and obliteration of the whole structure; not many glomeruli showing this stage could be detected.

The tubules were distorted by the fibrosis, many showed much fat in the epithelium, much of this fat being doubly refracting.

The blood-vessels, large and small, showed no change from normal; there was no intimal hyperplasia nor fatty change, and no splitting of the elastic laminae. The vessels of the spleen, lung, and skin were examined for evidence of arteriolar change and similarly showed no deviation from the normal.

*Case 111, Female.* Aged 19. Nothing of note in the past history until she suffered from 'influenza' in February 1922; thereafter there was swelling, first of the face, feet, and ankles, and later of the whole body, which continued until her admission on May 5, 1922. On admission the patient displayed a most intense general oedema; she was pallid, but made no complaint of pain, headache, or discomfort of any sort. The urine contained much albumin, blood, and many hyalo-granular casts.

In spite of urea medication by the mouth, the oedema, save for slight fluctua-



tions, remained much the same as on admission. The general condition of the patient showed little change until July, when vomiting commenced; at the same time the patient began to complain of headache and had spells of drowsiness. From this time on the general condition deteriorated and the oedema slowly but surely increased. It was now determined to try the effect of decapsulation of the kidney, and on August 16 this operation was performed upon the right kidney by Sir Cuthbert Wallace. The patient stood the operation well, and for a month after the operation the oedema was less and the general condition of the patient improved. By the end of September, however, the oedema was again on the increase, the headache and vomiting had returned, and the spells of drowsiness had become longer and more frequent. From this on the condition steadily became worse. Death occurred on November 21, 1922.

The results of the biochemical tests in this case were as follows:

May 19. Blood urea, 51 mg. per cent.  
Urea concentration after 15 grm. urea by mouth:  
1st hour, 1.24 per cent.

June 20. Blood urea, 109 mg. per cent. (Patient had been receiving urea medication by mouth to the extent of 45 grm. daily.)

August. 15. Blood urea, 49 mg. per cent. (Urea medication had been dropped.)

Urea concentration in urine after 15 grm. urea by mouth:  
1st hour, 0.65 per cent. in 25 c.c.  
2nd hour, 1.0 per cent. in 19 c.c.  
3rd hour, 0.9 per cent. in 10 c.c.

August 25. Blood urea, 88 mg. per cent.

August 30. Blood urea, 100 mg. per cent.

September 26. Blood urea, 106 mg. per cent.

November 14. Blood urea, 171 mg. per cent.

The blood-pressure showed a steady rise: May 19, 156/90; October 16, 156/128; October 21, 165/138; November 6, 175/125.

*Post mortem* the body showed marked general oedema; the pleural, pericardial, and peritoneal sacs were all filled with clear fluid. The heart was slightly enlarged (weight 13½ oz.), and the left ventricle a little hypertrophied; the valves and coronary vessels appeared normal. The right kidney, upon which the operation had been performed, was firmly adherent to the posterior wall of the abdominal cavity; the left kidney was somewhat larger than normal and slightly adherent to the perinephric tissue. The capsule of both kidneys was thickened, that of the right was firmly adherent to the surface of the organ as a result of the operation. The capsule of the left kidney, which had been subjected to no operative interference, stripped readily, leaving a smooth surface of a pale yellow colour mottled with red. On section both kidneys showed a cortex of rather more than normal depth, pale in colour, and displaying numerous yellowish striations. The medulla was deeply congested.

*Histology.* Thanks to the kindness of Sir Cuthbert Wallace, a small portion of the cortex was obtained from the kidney of this case at the operation for decapsulation performed on 16.8.22. The sections of this tissue are of particular interest as showing the processes active during life which were in course of producing the picture to be seen at death three months later. These sections showed a kidney so universally and apparently irreparably damaged that it was easy to prognosticate a fatal issue to the case.

The morbid changes affected interstitial tissue, glomeruli, and tubules alike, but the vessels remained quite unaffected. The interstitial tissue showed great relative increase in bulk, this increase being apparently very largely responsible for the general increase in size of the kidney. This increase was such that



throughout the kidney the tubules were widely separated from each other. Although some excess of fibrous tissue was present in this interstitial tissue, the increase in bulk was mainly accounted for by a dense infiltration with inflammatory cells (Fig. 6). These cells, for the most part, were of the mononuclear order, but a few pus cells were present, the whole process being obviously of an inflammatory nature. In the portions of kidney examined this round-celled infiltration was definitely diffuse, showing no signs of localization in foci around the glomeruli or elsewhere.

The glomeruli were universally the subjects of morbid change; the tufts were empty of blood and showed hyaline change and increase in the number of nuclei. In paraffin sections they appeared shrunken, but in frozen sections it was obvious that this was an artifact, for in these they completely filled the capsules. In both frozen and paraffin sections swelling of the endothelium of Bowman's capsule with adhesions between this and the tuft could be seen. This endothelial swelling was not accompanied by much actual proliferation, and no 'crescents' were seen.

Many of the tubules showed intense fatty change. In these tubules the epithelial cells had completely disappeared and were replaced by crystalline and amorphous masses of doubly refracting fatty substance. Many of the tubules contained masses of 'foam' cells—phagocytic cells containing droplets of this same doubly refracting fatty substance in their cytoplasm. Hyaline casts were present in the lumina of many of the tubules.

The sections from the kidney removed *post mortem* showed a condition which could be readily understood as the final stage of the morbid changes described above. The interstitial round-celled infiltration had almost completely disappeared, but the tubules were still widely separated by the fibrous tissue which had developed following upon the previously seen inflammatory condition (Fig. 7). This fibrous tissue was still somewhat cellular, but contained few round cells. The fibrosis, like the previous round-celled infiltration, was diffuse and had produced no puckering or granulation of the surface of the kidney, such as is seen in the typical 'contracted granular kidney'. It was none the less very evident.

The tubules appeared shrunken and distorted by the fibrosis. Many of them were in the condition described above, their epithelium replaced by amorphous and crystalline masses of doubly refracting fatty substance (Figs. 8 and 9, Plates 2 and 3). Others of the tubules showed very definite evidence of regeneration of the epithelium (Fig. 10). This regeneration in many instances had proceeded in rather an erratic fashion so as to result in the production of plicated masses of epithelial cells which it was difficult to believe could have any useful function. In others the regeneration had proceeded in a rather more orderly manner, and had resulted in the production of a new epithelial lining to the tubules concerned, differing only from the normal in being more columnar than is usual.

The glomeruli likewise showed a further advance upon the condition seen in the tissue removed during life (Fig. 11). All were affected. Many had been reduced to a mere hyaline lump with few or no remaining nuclei. Others were in the state described above, showing hyaline change of the tuft and increase in the nuclei. Others again showed marked proliferation of the endothelium of the capsule, with adhesions between this and the capsule. In contradistinction to the state of affairs in the tissue removed during life, well-formed endothelial crescents were present.

The vessels still showed no change from the normal.

*Sub-group 2.*

*Case 125.* Female. Aged 19. Measles in childhood. At age of 17 suffered from ulcers upon and swelling of the legs; these ulcers were presumed to be syphilitic and were treated as such. There was a history of syphilis in the parents, but the patient's Wassermann reaction was consistently negative. The ulcers disappeared under treatment, but reappeared a year later; on this occasion they were accompanied by very intense swelling of the legs. She was admitted to the Venereal Disease wards, where the ulcers healed under treatment and rest in bed; the oedema, however, persisted, together with much albumin in the urine. In February 1923 she was transferred to Professor MacLean's wards. At this time she showed marked oedema of the arms, legs, and face; the urine contained much albumin and many granular casts. Blood-pressure, 120/100.

The condition of this patient showed very little change during the remainder of her life in hospital until shortly before her death. The oedema decreased somewhat under urea medication by the mouth, but increased again when this was discontinued. Throughout the whole of her stay in hospital this patient suffered from severe diarrhoea. Towards the end of March her condition became insidiously worse; an evening rise of temperature appeared, but there was no complaint of pain or unusual discomfort. Death occurred on April 8.

The results of the biochemical tests in this case were as follows:

- February 19. Blood urea, 23 mg. per cent.  
 Urine urea, 1.06 per cent.  
 Urea concentration factor, 1/46.
- February 26. Blood urea, 82 mg. per cent.  
 Urine urea, 1.89 per cent.  
 Urea concentration factor, 1/23.

Up to this date the patient had been receiving 5 grm. of urea by the mouth thrice daily; this was now stopped.

- March 14. Blood urea, 27 mg. per cent.  
 Urine urea, 0.87 per cent.  
 Urea concentration factor, 1/30.  
 After 15 grm. of urea by mouth, urine urea:  
 1st hour, 0.85 per cent. in 100 c.c.  
 2nd hour, 1.2 per cent. in 100 c.c.  
 3rd hour, 1.4 per cent. in 32 c.c.

- March 28. Blood urea, 62 mg. per cent.  
 Urine urea, 1.0 per cent.  
 Urea concentration factor, 1/16.

- April 8. Blood urea, 117 mg. per cent.

*Post mortem.* The body was very oedematous; fluid was present in all the serous sacs. In the abdominal cavity long-standing adhesions were present along the colon and between the liver and diaphragm; the omentum was adherent in the right iliac fossa; in separating it from this attachment a certain amount of purulent matter was disclosed in the region of the appendix; this organ could not be found. The fluid in the peritoneal cavity was slightly turbid and contained some flakes of lymph; it was evident that there had been a low-grade and very chronic peritonitis. The kidneys were large and soft; weights, right 5 oz., left 5½ oz. The capsule stripped readily; on section the cortex was not reduced; the medulla was congested.

*Histology.* This kidney showed the changes characteristic of 'amyloid' degeneration, this being diffuse and accompanied by a slight but very definite amount of round-celled infiltration. The tubular epithelium showed marked

degenerative changes; in parts the nuclei had disappeared and the cells were obviously dead; elsewhere the cells were in a condition of 'cloudy' swelling; the cells in this condition showed minute droplets of doubly refracting fat at the end next to the basement membrane. Many of the tubules were greatly dilated, the epithelium of these dilated tubules being flattened; the lumina of many of the tubules contained waxy casts and phagocytic cells containing droplets of doubly refracting fat. The glomeruli (Fig. 12) were universally affected, and all more or less to the same degree. They showed no endothelial proliferation or other indications of an inflammatory process; but all exhibited large accumulations of the homogeneous 'amyloid' material. In all the differentiation of the loops of the tuft was to some extent lost, and some were reduced to mere homogeneous pastilles almost devoid of nuclei. The vessels showed the characteristic 'amyloid' deposit in the media, though this change was not so marked as in the glomeruli. Much doubly refracting fat was present throughout the sections. It has already been described in the bases of the degenerating epithelial cells of the convoluted tubules; much was also present in the cells of the fibrous supporting tissue and also in some of the glomeruli.

#### *Discussion.*

As already pointed out, there is one clinical and one histological feature common to all the cases described above, both of which are absent in nephritis of the 'primary chronic interstitial type'. Clinically, their common feature is the presence of marked oedema—not mere puffiness under the eyes or of the ankles, but a general intense anasarca. Histologically, the feature common to all the kidneys in the series is the presence in very large amounts of doubly refracting material giving the staining reactions of fat.

In all the cases this fatty material occurred in the epithelium of the tubules—more particularly in that of the convoluted tubules and of the ascending limb of the loop of Henle. In Cases 103, 125, and 133 it was also present to some extent, contained in polyblastic phagocytic cells, in the interstitial tissue. When it occurred in epithelium it was associated with morbid changes of the cells of varying degree. In some cases the cells appeared fairly normal, the only unusual feature being the presence of the doubly refracting material in the cytoplasm; in these cases it appeared as minute droplets between the nucleus and the basement membrane; in other cases the epithelial cells had practically disappeared, being almost entirely replaced by masses of the anisotropic material. In all cases phagocytic cells of the 'foam' type were present in the lumina of the tubules in greater or lesser numbers, their cytoplasm filled with droplets of the material and evidently in course of excretion in the urine.

The presence of this doubly refracting fatty substance in kidneys of the 'large white' type was first described at length by Stoerk (7), and has since been the subject of a good deal of investigation in Germany. As seen in fresh sections or scrapings from organs straight from the body it appears in the form of fluid spherocrystals, giving the characteristic cross of light when viewed between crossed Nicol prisms by means of the polarizing microscope; if, however, the kidneys be examined after having been kept for some time in Kaiserling's solu-

tion, the fatty material is found to have assumed the form of acicular crystals. From this form it can readily be reconverted to the fluid spherocrystal phase by gentle heating; on cooling and standing for some time, it returns to the solid crystalline state. The extent to which this material is present in the kidneys is indicated by Figs. 2 and 9, showing sections of kidneys photographed between crossed Nicol prisms. It is this substance which gives the peculiar greasy, yellowish appearance to the cut surface of kidneys of the 'large white' type, and which at autopsy is usually described as 'fat'. Under the name of 'myelin' kidney McNee (8) has described striking examples of kidneys of this type.

Stoerk (7) regarded this doubly refracting material as a lipid, and described it under the title of 'protagon'. The work of MacLean (9) and others showed that no such single substance as 'protagon' existed, and Adami and Aschoff (10) gave good grounds for believing that such deposits of doubly refracting fatty substances, no matter where they occurred in the tissues, consisted of the esters of cholesterol. Panzer (11) first definitely proved that the anisotropic material in kidneys of the type described above consisted of esters of cholesterol, and Windaus (12) carried the matter a step farther by demonstrating that, whereas in kidneys of this type the cholesterol occurring as such is normal in amount, that occurring in combination as the ester is enormously increased.

The insistence above upon the importance of degeneration of the tubular epithelium, together with the deposition of cholesterol esters, must by no means be taken as indicating that these are the only changes of importance present in kidneys of the 'large white' type. As pointed out above, glomerular changes were also present in all the kidneys, and on the basis of these glomerular changes it is possible to divide the cases into two groups.

In Group A the changes are of a degenerative nature and not such as to lead to any gross alteration in the size or morphology of the tuft. In Cases 103 and 133 (Figs. 1 and 4) they consist merely of swelling of the loops, leading to loss of differentiation of the structure of the tuft, together with an apparent increase of the nuclei, which, moreover, do not take the nuclear stain in a normal manner. In Case 130 (Fig. 3) the glomerular change is more marked; the loss of differentiation of the structure of the tufts is here complete, the nuclei are diminished in numbers, and the whole organ presents a homogeneous hyaline appearance; in all cases in this group evidence of inflammation is entirely absent from the glomeruli. In all these cases it is to be particularly noted that all the glomeruli are equally affected, and all in the same stage of morbid affection.

Clinically, as pointed out above, all these cases were characterized by the fact that they showed no tendency to retention of urea or to hypertension, and that macroscopic haematuria was not present.

In the second group the glomerular changes were much more severe, leading to marked morphological alteration. As pointed out above, two types of change were presented. In Cases 94 and 111 these were definitely inflammatory in nature, as shown by proliferation of the endothelium, adhesion between the loops of the tuft and the capsule, and the presence of round cells (Figs. 5 and 11). In

Case 125 the profound alteration of the glomeruli was due to the deposition of 'amyloid' material; in this case round cells were to some extent present in the interstitial tissue, but their distribution was not markedly periglomerular.

Clinically, these cases in the second group were all characterized by macroscopic haematuria, by a progressive inability to excrete urea, and by hypertension, as indicated during life by the blood-pressure readings, and after death by the presence of cardiac hypertrophy. Case 125 belongs to rather a different category from Cases 94 and 111, and it is to these two latter that it is particularly desired to draw attention. In these two cases the glomerular changes, as can be seen from Figs. 5 and 11, are obviously inflammatory; moreover, as these illustrations show, they closely resembled the alterations seen in the glomeruli in the contracted granular kidneys from cases of 'primary chronic interstitial nephritis', of the type described by Shaw Dunn and others as showing secondary inflammatory changes. These are the cases, above all others, clinically marked by inability to excrete urea. The presence in Cases 94 and 111, in kidneys from an entirely different class of case, but also in association with urea retention, of these same glomerular lesions, coupled with the fact of their absence in Cases 103, 130, 133, in which there was no azotaemia, would seem to point to a close connexion between glomerular lesions and urea retention.

But little light is thrown upon the vexed question of aetiology by the consideration of the above cases. One thing, however, is clear, and that is that various factors may be responsible for the causation of the clinical picture of 'hydraemic' subacute parenchymatous nephritis. Leaving aside Case 125, in which 'amyloid' degeneration was at the root of the kidney changes, two entirely different sets of pathological processes are to be seen in the cases described under Group A, and in Cases 94 and 111 under Group B. In the cases described under Group A the changes are degenerative, there being no evidence of inflammation; as to the cause of this degenerative process there is no hint. In Cases 94 and 111, as already pointed out, there is plentiful evidence of the presence of an inflammatory process; it is noteworthy that in Case 94 there was a history of a previous attack of influenza; in this case the portions of the kidney removed during life showed histological appearances strongly resembling those described by Chapman (13) in late scarlatinal kidneys.

The evidence, both clinical and pathological, as set forth above, seems to indicate that these two last cases, had not death supervened, were on the way to becoming cases of 'secondary chronic interstitial' nephritis, with urea retention, hypertension, and contracted kidneys. On the other hand, there is no evidence that the cases under Group A were tending in this direction. On the face of it, it would appear that there exist at least two types of 'hydraemic' nephritis, and that only one of these, that associated with inflammatory changes in the glomeruli, tends to pass into the azotaemic 'chronic interstitial' type.

Volhard and Fahr (14) some years ago made an attempt to reduce all forms of nephritis to three main types, depending upon three dominant clinical features. Their three dominant clinical features were hypertension, haematuria, and oedema,



and, as the morphological basis of these symptoms, they recognized vascular change, glomerulitis, and tubular degeneration respectively. Their views have had a considerable vogue in Germany and in America, where there is still a tendency to consider nephritis of the third type as a separate entity under the title of 'nephrosis'. All the cases described above would, on clinical grounds, fall under this head. Consideration of the histological reports given above, however, shows that the conditions described can hardly be looked upon as dependent upon a pure tubular lesion; in every case some degree of glomerular damage is present, in Group A of a degenerative nature, in Group B of an inflammatory nature and severe.

It is true that in all these cases oedema and marked tubular degeneration are common features. As, however, Fahr (15), who has latterly dissociated himself from the views which he formerly expressed jointly with Volhard, has himself pointed out, it is difficult, in the face of experimental data, to look upon simple tubular degeneration as the cause of the oedema. Destruction of the epithelium of the renal tubules, such as may be brought about in experimental animals, does not result in oedema; it is true, as Boycott (16) has pointed out, that oedema may be produced in such animals by the injection of large quantities of fluid, but this is hardly analogous to the state of affairs in the human patient. Moreover, very extensive tubular degeneration may occur in nephritis of the 'chronic interstitial' type without the supervention of oedema. The factor common to all cases showing oedema is not so much the mere presence of degeneration of the tubular epithelium as the occurrence in it of the massive deposits of cholesterol esters described above; this factor, moreover, is absent from all those cases not showing oedema.

That there is some causal connexion between the deposition of the cholesterol esters and the occurrence of oedema seems to be indicated by recent German work. Thus Strauss (17), Stepp (18), and others have demonstrated the apparently constant occurrence of a very abnormally high cholesterol content in the blood of nephritic patients of 'hydraemic' type, as opposed to low or normal figures in patients not showing oedema. Stepp has carried the matter even farther by producing figures indicating that the cholesterol content of the blood varies directly with the oedema.

So strongly has the constant occurrence of the deposits of cholesterol esters in kidneys of the 'large white' type impressed Fahr (15), that he has suggested that the process underlying the production of 'renal' oedema is not the damage to the kidney tissue at all, but a change in the capillaries of the 'Unterhautzellgewebe'. Such opinions must, for the present, remain entirely speculative, but it is possible that the time is near when the reticulo-endothelial system, of which the relationship to cholesterol metabolism has been demonstrated by the work of Anitschkow (19) and Chalatow (20), may have to be included within the pathological picture of hydraemic nephritis.



*Summary and Conclusion.*

1. Six cases of nephritis of 'subacute parenchymatous' type, all associated with intense oedema, are described in respect of clinical features and response to certain tests of renal function during life and the pathology of the kidneys after death.

2. Histologically, the kidneys in all cases showed both glomerular and tubular lesions.

3. On the basis of the glomerular changes it was possible to divide the cases into two groups.

In Group A the glomeruli showed more or less degeneration without marked morphological change. These cases during life showed no urea retention or hypertension.

In Group B the glomeruli showed gross morphological changes, in two cases of an inflammatory nature, and in one due to 'amyloid' change. These cases all showed increasing inability to excrete urea, and progressive hypertension.

It is suggested that the healing process may, under favourable circumstances, be complete in cases of the type described under Group A, whereas in those of the type described under Group B it will tend to the production of the 'secondarily contracted' kidney associated with azotaemia and hypertension.

4. The tubular lesions were the same in both Groups A and B, and consisted in degeneration of the epithelium, with deposition of masses of cholesterol esters.

5. Attention is drawn to the fact that this deposition of cholesterol esters is the one histological factor common to the kidneys in all cases of nephritis of 'hydraemic' type. The significance of this fact in relationship to the production of oedema is briefly discussed.

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## REFERENCES.

1. Dyke, S. C., *Quart. Journ. Med.*, Oxford, 1922-23, xvi, 1.
2. Jores, L., *Wesen und Entwicklung der Arteriosklerose*, Bonn, 1903.
3. Evans, G., *Quart. Journ. Med.*, Oxford, 1920-2, xiv, 215; *Brit. Med. Journ.*, 1923, i, 454, 502, 548.
4. Gull, Sir William W., and Sutton, H. G., *Med. Chir. Trans.*, Lond., 1872, lv, 273.
5. MacLean, H., *Brit. Med. Journ.*, 1922, ii, 1067.
6. Shaw Dunn, J., *Brit. Med. Journ.*, 1922, ii, 1166.
7. Stoerk, *Über Protophag und über die grosse weisse Niere*, Wien, 1900.

8. McNee, J. W., *Journ. Path. and Bact.*, Edinb. and Lond., 1922, xxv. 425.
9. MacLean, H., *Lecithin and Allied Substances: the Lipins*, Lond., 1918.
10. Adami, J. G., and Aschoff, L., *Proc. Roy. Soc., B.*, Lond., 1906, lxviii. 359.
11. Panzer, T., *Zeitsch. für Physiol. Chem.*, Strassb., 1906, xlviii. 519.
12. Windaus, *Deutsch. med. Woch.*, 1919, xlv. 1229.
13. Chapman, E. S., *Journ. Path. and Bact.*, Edinb. and Lond., 1906, xi. 276.
14. Volhard and Fahr, *Die Brightsche Krankheit*, Berlin, 1914.
15. Fahr, T., *Virchow's Archiv f. Path. Anat.*, Berlin, 1922, ccxxxix. 32.
16. Boycott, A. E., *Journ. Path. and Bact.*, Camb., 1913-14, xviii. 11.
17. Strauss, H., *Med. Klin.*, Berlin, 1921, xvii. 20.
18. Stepp, W., *Deutsch. Arch. für Klin. Med.*, 1918, cxxvi. 439.
19. Anitschkow, N., *Beitr. zur path. Anat. und zur allg. Path.*, Ziegler, Jena, 1914, lvii. 201.
20. Chalataw, S. S., *Die anisotrope Verfettung im Lichte der Pathologie des Stoffwechsels*, Jena, 1922.

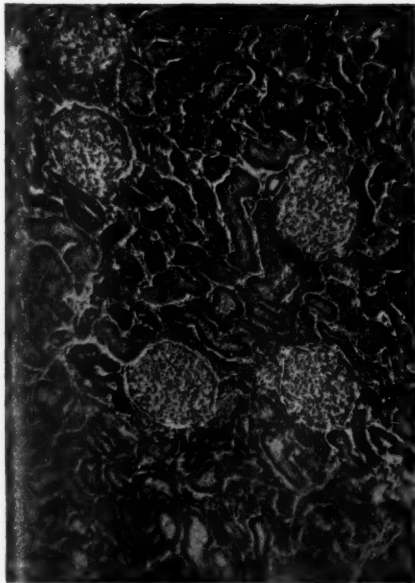


FIG. 1. Case 103. Glomeruli showing moderate degree of degenerative change evidenced by loss of differentiation of the tuft with apparent increase of nuclei. The surrounding tubules contain a large quantity of fat-staining material. Frozen section. Stain, haematoxylin and Sudan III.

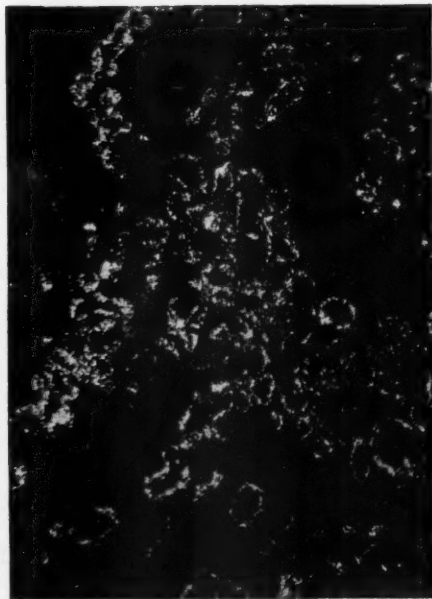


FIG. 2. Case 180. Portion of cortex in unstained frozen section viewed between crossed Nicol prisms, showing tubules outlined by deposits of doubly refracting fatty material in the degenerated epithelium.

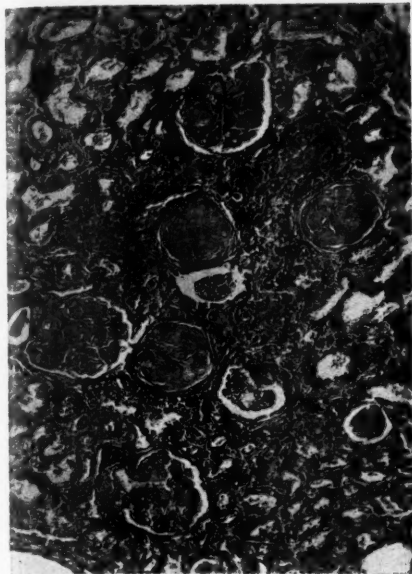


FIG. 3. Case 130. Glomeruli showing marked degeneration of the tuft. Paraffin section. Stain, haematoxylin and eosin.

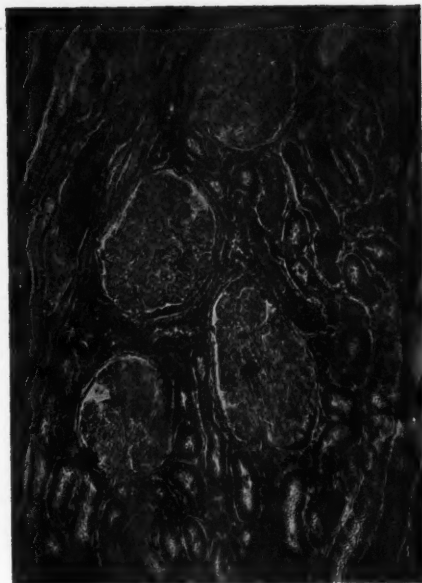


FIG. 4. Case 133. Glomeruli showing moderate degree of degenerative change. Frozen section. Stain, haematoxylin and Sudan III.



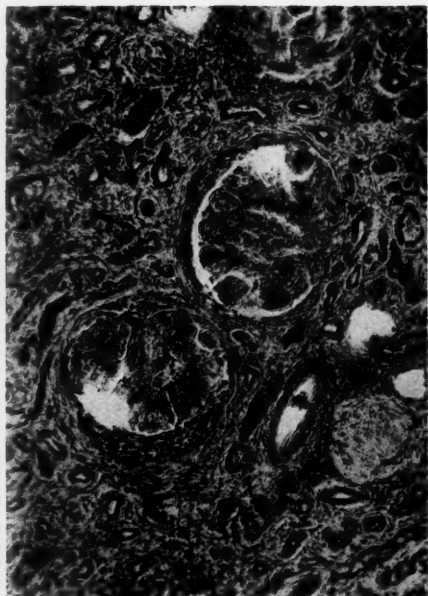


FIG. 5. Case 94. Glomeruli showing inflammatory changes as evidenced by presence of endothelial crescents and ultimate scarring. Frozen section. Stain, haematoxylin.

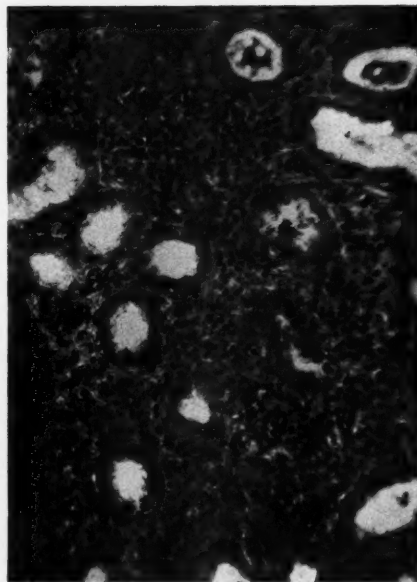


FIG. 6. Case 111. Portion of kidney removed three months before death, showing intense interstitial round-celled infiltration causing wide separation of the tubules. Paraffin section. Stain, eosin and methylene blue.



FIG. 7. Case 111. Portion of cortex of kidney removed *post mortem*, showing disappearance of round cells and their replacement by fibrous tissue which still causes wide separation of the tubules. Paraffin section. Stain, haematoxylin and eosin.

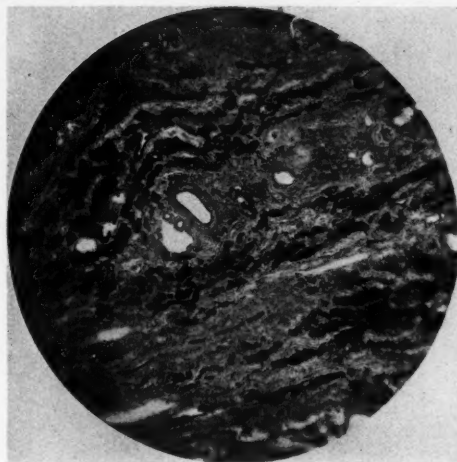


FIG. 8. Case 111. Portion of boundary zone of kidney removed *post mortem*, stained with OSO, showing massive deposits of fat-staining material in the tubules. Frozen section.







FIG. 9. Case 111. Similar section to Fig. 8, unstained and photographed between crossed Nicol prisms, showing doubly refractive nature of the fat-staining material.

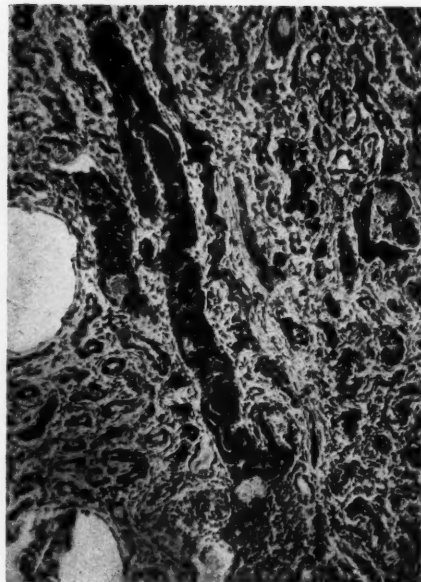


FIG. 10. Case 111. Portion of kidney removed *post mortem*, showing regeneration of tubular epithelium. Note folded and plicated arrangement of newly-formed epithelial lining of the tubule. Frozen section. Stain, haematoxylin and Sudan III.

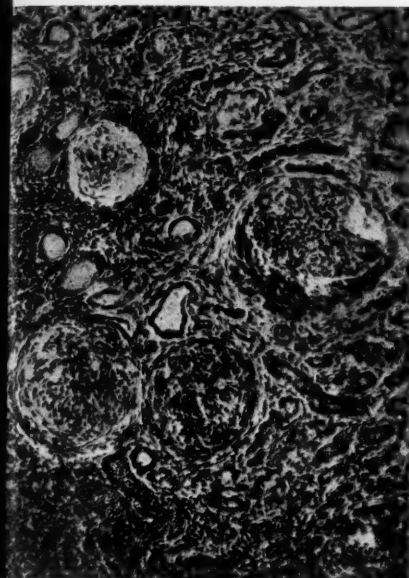


FIG. 11. Case 111. Portion of cortex of kidney removed *post mortem*, showing various stages of glomerular damage. In three of the glomeruli the inflammatory reaction is proceeding as indicated by swelling of the tuft, endothelial proliferation, and adhesions between the loops of the tuft and the capsule. In the fourth, scarring has taken place. Note the interstitial round-celled infiltration. Frozen section. Stain, haematoxylin.

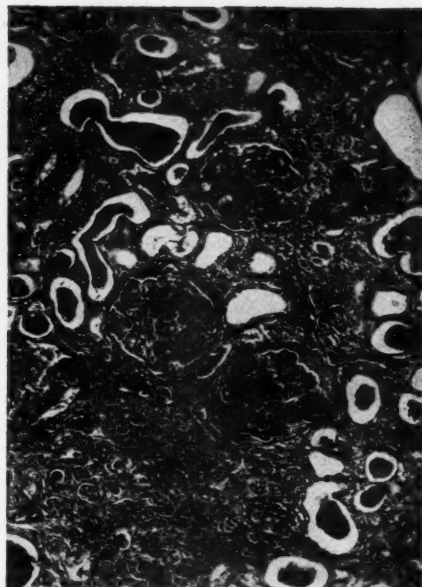


FIG. 12. Case 125. Glomeruli showing deposition of 'amyloid' material. Paraffin section. Stain, haematoxylin and eosin.



## SPONTANEOUS SUBARACHNOID HAEMORRHAGE

By C. P. SYMONDS

(From the Neurological Clinic, Guy's Hospital)

With Plate 4

### *Introductory and Historical*

THE commonest cause of haemorrhage into the subarachnoid space being injury to the head, the term 'spontaneous'<sup>1</sup> is taken to describe those instances of subarachnoid haemorrhage which are of non-traumatic origin. Such cases would seem to be of not uncommon occurrence, yet, save for occasional comments, the literature of the subject may be said to have developed only within the past fifty years.

Wilks (76), in 1859, gave a brief account of the post-mortem appearances in four instances of spontaneous subarachnoid haemorrhage, and in his *Diseases of the Nervous System*, published in 1883 (75), has a note upon the pathology and symptoms of the condition, with a short clinical account of three further cases. Gintrac, in his text-book *Maladies de l'appareil nerveux*, published in 1869 (35), has a chapter upon meningeal haemorrhage which includes thirty-four instances of subarachnoid haemorrhage briefly described, with a note upon the aetiology, pathology, and symptomatology of the condition. The collection includes thirty-two cases previously reported, together with two of his own. This account, though undoubtedly one of the most important early contributions to the literature of the subject, appears to have escaped the attention of later writers. Hayem's (42) thesis of 1872 upon 'Hémorrhagies intrarachidiennes' covers much the same ground as that described by Gintrac, but contains an account of four new cases.

From this time forward no original paper of note appears to have been published upon the subject until the advent of lumbar puncture, in the beginning of the present century, permitted the diagnosis of subarachnoid

<sup>1</sup> The title of this paper would seem to require a word of explanation. The word 'spontaneous' is apt to be employed in medicine, together with its synonym 'idiopathic', as a remedy against the pangs of ignorance. Thus, Pasteur's critics employed it when they talked of 'spontaneous generation'. In its present connexion the term has come to have a definite usage in the sense of 'non-traumatic', and as such I have accepted it, on the understanding that it implies no more.

haemorrhage at the bedside, and revealed its occurrence in certain cases which recovered.

Froin's (32) thesis of 1904, entitled *Les hémorrhagies sous-arachnoïdiennes*, with its careful studies of the blood-stained cerebro-spinal fluid, both immediately after the haemorrhage and in process of haemolysis, marked a definite step forward in our knowledge of this condition, and inspired numerous other observations upon the Continent.

Ehrenberg (24) of Stockholm in 1912, presenting the detailed clinical data of two cases under his observation, reviewed the histories of twenty-nine instances from the literature, and concluded that the clinical signs of the condition were sufficiently definite to permit grouping under four heads: (1) the cases with pure meningeal symptoms; (2) cases with an apoplectiform onset; (3) cases with apoplectiform onset proceeding to coma, and subsequently developing meningeal signs; (4) cases with apoplectiform onset proceeding to coma and death without the development of other signs. Ehrenberg also remarked upon the comparatively low age incidence of the condition as compared with that of cerebral haemorrhage, and briefly discussed the pathology, which he was compelled to admit was obscure.

Meanwhile there had been accumulating a mass of literature, chiefly derived from post-mortem records, concerning intracranial aneurysms as a cause of fatal subarachnoid haemorrhage. This was fully reviewed by Fearnside (29) in 1916, who added an account of forty-four new cases. Commenting upon the pathology of the condition he remarked that intracranial aneurysms may be divided into two groups according to their inflammatory or non-inflammatory origin. In the latter group the cause of the aneurysm is degeneration of the media, which is frequently associated with generalized arterial degeneration and cardiac hypertrophy. In a number of cases, however, intracranial aneurysms of this group are discovered in young persons without evidence of cardio-vascular disease. In explanation of these cases the suggestion was first put forward by Eppinger (25), and adopted by Wichern (72), that the breach in the media is due to an inborn defect in the arterial wall, a conclusion reached independently by Turnbull (68, 69) in a general study of arterial disease.

Fearnside remarked upon the value of stiffness of the neck as a diagnostic sign after rupture of aneurysm in the posterior fossa, but his study of the clinical picture of a leaking aneurysm is without reference to that of subarachnoid haemorrhage as a whole.

Ingvar (43), in 1918, reported five new cases of subarachnoid haemorrhage, one of them being due to a ruptured aneurysm. He discussed and amplified Ehrenberg's clinical observations with some valuable additional notes of his own, especially upon the occurrence of fever.

Goldflam (36), in 1923, has discussed afresh the symptomatology and pathology of spontaneous subarachnoid haemorrhage with reference to the work of Ehrenberg, but not to that of Ingvar. He mentions thirteen cases of his own (without relating full particulars) and reiterates the comment of Ehrenberg

upon the low age incidence. Ten of Goldflam's cases occurred in persons below the age of 30. He adds the significant argument that in these cases there could be no question of arterial disease or aneurysm as the cause, since all the patients were previously healthy and free from disease at the time of the attack; from which one may infer that the observations of Eppinger, Wichern, Turnbull, and Fearnside upon aneurysms in young people have escaped his notice.

In 1923 (65) I reported five cases of subarachnoid haemorrhage with acute meningeal symptoms, two of which were proved at post-mortem to be due to ruptured aneurysm. I concluded that in the other three cases, in one of which the post-mortem examination was incomplete, while the other two recovered, the cause was probably also a leaking aneurysm.

It appears then that whereas on the Continent the clinical appearances of spontaneous subarachnoid haemorrhage have been carefully studied, the foreign literature has not stimulated much interest in this country, and the subject has received comparatively little attention. On the other hand, the relatively frequent occurrence of aneurysm as a cause of fatal subarachnoid haemorrhage, as demonstrated especially by Turnbull and Fearnside in this country, has not engaged the attention of foreign workers.

The basis of the present paper is an attempt to correlate these two sets of observations, and by so doing to obtain a clearer view of the whole subject of spontaneous subarachnoid haemorrhage, both in its clinical and its pathological aspects.

Three new cases will also be reported and reviewed in the light of previous observations and reflections.

As a preliminary measure I shall consider briefly such anatomical relations of the subarachnoid space as may serve to elucidate the subsequent discussion.

#### *Anatomical Considerations.*

Following Froin, we may consider the arachnoid membrane as consisting of two layers—parietal and visceral. The parietal layer consists of a sheet of endothelial cells lining the internal surface of the dura mater. The visceral layer consists of a thin transparent sheet of connective tissue covered with endothelial cells which, upon its external surface, is separate from, but lies closely applied to, the parietal layer. Internal to this again is the pia mater, which is attached to, and therefore follows exactly, the surface of the brain and spinal cord.

The potential cavity existing between the parietal and visceral layers of the arachnoid is commonly known as the subdural space. That which lies between the arachnoid and the pia mater is the subarachnoid space. This latter space is normally occupied by the cerebro-spinal fluid. Although it is a free space in the sense that all parts of it are in direct communication with one another, it is to some extent broken up by innumerable fine trabeculae passing between the arachnoid and pia mater, which support the vessels running therein. Through



the roof of the fourth ventricle the subarachnoid space is in direct communication with the cerebral ventricles. In a caudal direction it extends as far as the first or second sacral vertebra. Into this space blood may readily gain entrance from four different sources. (i) An effusion originating within the subdural space (as commonly results from traumatic laceration of the veins leading from the cerebral cortex to the great sinuses) may rupture the visceral layer of the arachnoid membrane and gain entrance to the subarachnoid space in this wise. (ii) A haemorrhage into the superficial parts of the nervous substance may break through the pia mater into the subarachnoid space. (iii) A deeply situated cerebral haemorrhage may rupture into one of the ventricles, and thence the effusion may find its way into the subarachnoid space through the roof of the fourth ventricle. (This and the preceding variety have been referred to by Froin as examples of *cerebro-meningeal haemorrhage*.) (iv) The haemorrhage may be derived from one of the vessels lying in the subarachnoid space itself.

There are a few anatomical points of further importance in relation to the spread of subarachnoid haemorrhage.

Upon the surfaces of the cerebral hemispheres the visceral layer of the arachnoid is relatively closely applied and attached to the pia mater covering the cerebral gyri, but bridges over the sulci without descending into them. At the base of the brain, however, the arachnoid is but loosely attached to the pia mater, so that the circle of Willis lies in a clear lake of cerebro-spinal fluid (consisting of the cisterna basalis and cisterna pontis). This lake is in free communication on the one hand with the subarachnoid spaces surrounding the superficial cerebral vessels which lie in the cerebral sulci, and on the other hand with the subarachnoid space surrounding the medulla and spinal cord.

From a consideration of these facts it is easy to understand that a haemorrhage into the basal subarachnoid space readily finds entrance to the spinal subarachnoid space, and in an upward direction floods the cerebral sulci, the narrow spaces upon the gyri being penetrated with greater difficulty. Thus when the haemorrhage has originated at the base and has been of slow development the appearance of the brain may suggest at first sight that there has been a general oozing from all the main vessels.

On the other hand, a haemorrhage originating from the surface of one of the cerebral hemispheres spreads less readily, being restricted laterally by the shallow supragyral spaces. Such a haemorrhage will gradually empty itself into the basal lake along the lines of the main cortical vessels by way of the sulci, but if at the onset the effusion be rapid, the restricted outflow may result in a local increase of pressure with damage to the cerebral cortex; or the pressure may rise to a point at which the effusion bursts through the pia mater into the nervous substance—the accident termed by Froin *meningo-cerebral haemorrhage*.

Between the lateral and third ventricles and the general subarachnoid space the channel lies through the narrow Sylvian aqueduct. Hence it is only with difficulty and at a slow rate that a ventricular haemorrhage gains entrance into the general lake of cerebro-spinal fluid.



The fine meshwork of trabeculae permeating the subarachnoid space doubtless tends in all cases of subarachnoid haemorrhage to promote coagulation at and around the point of leakage. This tendency to localized clotting is, however, most apparent in the case of cortical and ventricular haemorrhages, owing to the obstacles to diffusion. In the case of a severe basal haemorrhage the extravasation commonly becomes spread out before clotting has time to occur, so that the cerebral sulci and spinal subarachnoid space, as well as the basal cisterns, become filled with a thin layer of coagulum.

The following observations upon the clinical and pathological aspects of spontaneous subarachnoid haemorrhage are derived from a study of 124 cases recorded by various authors, together with their several comments, and three new observations of my own, to be related presently. Of the total number of 127 cases, seven have come within my own observation. I have been careful to include only those cases in which the diagnosis of subarachnoid haemorrhage was proved, either at autopsy, or by means of lumbar puncture. These are all cases of primary subarachnoid haemorrhage, coming within group (iv) of the previous page. Those of group (i), being traumatic, are excluded from present consideration by the title of my paper, and I have omitted from my collection all cases in which intracerebral haemorrhage has ruptured either into the meninges or the ventricles (groups (ii) and (iii)) for reasons which will be made clear in the section upon pathology.

### *Clinical.*

The clinical evidence of subarachnoid haemorrhage may be considered under two heads: first, that derived from observation of the patient at the bedside; second, that obtained from investigation of the cerebro-spinal fluid. For the purpose of the present discussion, however, it will prove convenient to reverse this order. The changes to be observed in the cerebro-spinal fluid presenting few variations, and being capable of a simple interpretation, will be considered first, after which an attempt will be made to set forth the more complex problem of clinical classification with illustrative examples of the groups proposed. Finally, the ophthalmoscopic appearances in certain of these cases, and the phenomenon of 'massive albuminuria' in others, will be considered separately as deserving special attention.

1. *The cerebro-spinal fluid.* After the lapse of twenty years there is little to be added to the observations and conclusions of Froin. Shortly after the onset of the haemorrhage the fluid obtained by lumbar puncture appears on withdrawal to be mixed with blood, and is usually under increased pressure. If this fluid be collected in a series of three test-tubes, the same degree of admixture is to be observed in each. The proportion of blood to cerebro-spinal fluid will vary, on the one hand, according to the severity of the leakage, and on the other hand according to the situation of the ruptured vessel. Blood extravasated into one of the basal cisterns will find its way more readily to the site of lumbar puncture

than an effusion originating from the surface of one of the cerebral hemispheres or from the wall of one of the lateral ventricles. Thus the colour of the fluid when first withdrawn may vary from an opalescent pink to that of pure blood—the highest count of red cells per c.mm. which I have found recorded being 3,380,000. On being allowed to stand in the test-tube this sanguineous fluid forms no coagulum. The red cells sink to the bottom of the tube, and the clear supernatant fluid appears coloured by the presence of altered blood pigments. This colour varies from a pale orange or brown to golden yellow. Subsequently it undergoes changes together with the other elements in the fluid, which I shall refer to later.

Thus the distinctive macroscopic features of the cerebro-spinal fluid in subarachnoid haemorrhage are three: (1) An even admixture of blood, which is the same in a series of specimens collected at the same puncture; (2) absence of coagulum; (3) orange, brown, or yellow coloration of the clear supernatant fluid, which is apparent when the red cells have been allowed to sink to the bottom of the tube. None of these three features is to be observed in cerebro-spinal fluid contaminated by the accidental injury of a vein during lumbar puncture. Here, on the other hand, when the fluid is obtained in a series of tubes the first is seen to be more deeply stained than the last. On standing in the test-tube the fluid forms a coagulum, and the clear fluid in the upper portion of the tube remains colourless.

The explanation offered by Froin for these differences appears to be satisfactory. In subarachnoid haemorrhage the effusion of blood forms a coagulum at and around the site of the leakage. The proportion of red cells entangled in this coagulum varies somewhat according to the severity of the leakage and its situation. If the latter be in one of the basal cisterns where the circulation of the cerebro-spinal fluid is free, large numbers of red cells are liberated, and rapidly become diffused throughout the subarachnoid space. If, at the other extreme, the site of the haemorrhage be in the lateral ventricle, the path of outflow through the iter is relatively narrow and the great majority of red cells are entangled in the clot. Such as do find their way to the basal cisterns rapidly diffuse throughout the great subarachnoid lake.

Hence two of the characteristic features of the fluid obtained at lumbar puncture—the even admixture of the red cells, and the absence of coagulum.

The coloration of the supernatant fluid appears to be due to pigments derived from the red cells in process of destruction. This process of haemolysis is most active a few days after the initial effusion, and it is at this time therefore that the colour change is most remarkable. The tint is variable. In the earliest stages there may be very little or no coloration. The rose-yellow or brownish tint appears to coincide with the height of haemolysis in a large effusion, and the spectroscope shows the oxyhaemoglobin or haemoglobin absorption bands; this colour yields later to a golden yellow which gives the chemical reactions proper to bile pigments. In the case of a small effusion the colour may never be darker than golden yellow.

The microscopic changes which are to be observed in the sanguineous fluid have been carefully studied by Widal (74), Froin, and others.

In the earliest stage the number of white cells in proportion to the reds is that met with in the blood. Later there is an increase in the white cells at first, especially of polymorphs, large mononuclears, and eosinophils, later of lymphocytes; and a small increase of lymphocytes may still be observed when the red cells have disappeared from the fluid, and this is clear and colourless.

*Pari passu* with the haemolysis in the cerebro-spinal fluid there is an increase of bile pigment in the blood and urine.

The following examples abstracted from Froin's monograph serve to illustrate these observations:

*Froin, Obs. III, p. 65.* A woman, aged 70, was taken suddenly ill with cerebral symptoms. She died on the eighth day of her illness.

The autopsy revealed extensive subarachnoid haemorrhage from rupture of the left posterior cerebral artery close to its point of origin. All the cerebral vessels showed gross degenerative changes. The cerebro-spinal fluid was obtained on the first, third, fifth, and seventh days of her illness. On the *first day* 15 c.c. were collected in three tubes. The colour was a bright red, uniform in the three tubes. On centrifugalizing there was a large deposit of blood-cells. The supernatant fluid was yellow, slightly opaque. The cell count showed 1,263,300 red cells; 2,100 white cells. The red cells were of normal appearance. The differential count was:

Lymphocytes	.	.	.	.	.	.	15.68
Polynuclears	.	.	.	.	.	.	52.94
Large mononuclears	.	.	.	.	.	.	31.37

*Third day.* 15 c.c. in three tubes. Colour bright red: uniform in all tubes. Centrifugalized specimen: large sediment of blood-cells. Supernatant liquid bright yellow with a slight greenish tinge. Cell count: reds 2,030,000; whites 1,900. Cytology: red cells of normal shape. Differential white count:

Lymphocytes	.	.	.	.	.	.	17.89
Polynuclears	.	.	.	.	.	.	64.11
Eosinophils	.	.	.	.	.	.	2.10
Large mononuclears	.	.	.	.	.	.	15.78

Spectroscopy: the right half of the spectrum blotted out, the oxyhaemoglobin bands faintly visible. Bile pigments: Gmelin's reaction well marked in cerebro-spinal fluid, also present in blood-serum.

*Fifth day.* 15 c.c. in three tubes: colour cherry-red: uniform in all tubes. Centrifugalized specimen: sediment less than before; supernatant fluid very yellow. Cell count: reds 517,500, of which 17,500 were spherical and opaque. Much cell debris. Whites 400. Cytology: reds for the most part normal; some crenated. Differential white count:

Lymphocytes	.	.	.	.	.	.	8.47
Polynuclears	.	.	.	.	.	.	9.32
Eosinophils	.	.	.	.	.	.	8.46
Large mononuclears	.	.	.	.	.	.	72.87
Haemomacrophages	.	.	.	.	.	.	0.84

Spectroscopy: right half of the spectrum blotted out, oxyhaemoglobin bands not seen. Bile pigments: Gmelin's reaction well marked in cerebro-spinal fluid

and blood-serum. Both fluids have a greenish yellow tinge. Urobilin: present in urine.

*Seventh day.* 15 c.c. in three tubes: cherry-red colour, uniform in all three. Centrifugalized specimen: sediment less; supernatant fluid rosy yellow. No coagulum or filaments of fibrin. Cell count: reds 450,000. Much cell debris. Whites 700. Cytology: reds, many normal; some crenated. Differential white count:

Lymphocytes . . . . .	15.54
Polynuclears . . . . .	48.73
Eosinophils . . . . .	0.84
Large mononuclears . . . . .	34.87

Spectroscopy: oxyhaemoglobin bands present. Bile pigments: Gmelin's reaction less marked in cerebro-spinal fluid. Urobilin: test positive in urine; negative in cerebro-spinal fluid.

*Froin, Obs. VI, p. 90.* The patient, a healthy woman, aged 22, was seized suddenly with headache and vomiting on June 27, admitted to hospital June 28. Severe headache, neck retraction, and positive Kernig's sign present. Under observation the temperature showed an irregular rise up to 101° F. She gradually recovered and left the hospital on July 30. On August 8 she remained well. The salient features of the cerebro-spinal fluid in this case were as follows:

*Second day.* 15 c.c. in three tubes; colour uniformly pink. Centrifugalized specimen: small sediment, yellow fluid; no coagulum. Cell count: reds 20,333. Cytology: many crenated red cells. Relative increase of white cells. Differential count of white cells:

Lymphocytes . . . . .	25
Polynuclears . . . . .	50
Large mononuclears . . . . .	25

Spectroscopy: oxyhaemoglobin spectrum just visible. Bile pigments: Gmelin's reaction negative in blood and cerebro-spinal fluid.

*Third day.* Cerebro-spinal fluid taken directly into culture tubes: all remained sterile. Differential white cell count in cerebro-spinal fluid:

Lymphocytes . . . . .	37
Polynuclears . . . . .	50
Large mononuclears . . . . .	13

*Tenth day.* 15 c.c. in three tubes: colour markedly yellow: uniform in all tubes. Centrifugalized specimen: very small sediment: no coagulum. Cell count: reds 107; whites 40. Many crenated reds and much cell debris. Cytology: large numbers of lymphocytes and large mononuclears. Not more than five or six polynuclears seen, of which three were eosinophils.

Spectroscopy: negative. Bile pigments: Gmelin's reaction negative.

*Seventeenth day.* 15 c.c. in three tubes: colour uniformly yellow, but less so than before. Centrifugalized specimen: punctiform sediment. Cell count: red cells 6; white cells 9. Much cellular debris. Cytology: red cells poorly stained. Many lymphocytes. A few large mononuclears.

*Thirty-third day.* Colour very slightly yellow: small sediment: no coagulum. Differential count of white cells:

Lymphocytes . . . . .	81.48
Polynuclears . . . . .	3.70
Large mononuclears . . . . .	10.18
Haemomacrophages . . . . .	2.95

*Forty-third day.* Fluid clear and colourless. Slight lymphocytosis still present.

2. *The symptoms and signs of subarachnoid haemorrhage.* An account of the symptoms and signs of subarachnoid haemorrhage is perhaps best prefaced by a theoretical consideration of the factors concerned in their production.

The extravasation of any large quantity of blood into the subarachnoid space produces results which are in the main due to its mechanical effects, but are partly derived from the inflammatory reaction which accompanies the presence of free blood in a serous cavity. It will therefore be convenient to consider separately the mechanical and irritative effects of such an effusion.

A. *Mechanical effects.* The first effect produced by a ruptured meningeal vessel must necessarily be local pressure upon the nervous substance in its immediate neighbourhood. According to the accepted laws of neuro-pathology the resulting anoxaemia will give rise at first to exaltation, and subsequently to depression of the functions of the part affected. Thus an effusion upon the surface of the motor cortex would cause first Jacksonian epilepsy, subsequently hemiparesis upon the opposite side of the body. Owing, however, to the relatively free communication which exists between all parts of the subarachnoid space, the extravasation rapidly tends to become diffused, and a great increase of local pressure is converted into a moderate increase of general pressure. Thus the *local* effects of a subarachnoid haemorrhage are apt to be of a transient character, leading either to rapid recovery—if the haemorrhage is non-progressive—or to the development of signs of a general increase of intracranial pressure.

Owing to the anatomical facts already considered, haemorrhage originating at the base of the brain is likely to become rapidly diffused, and in these cases, therefore, signs of local pressure, either upon cranial nerves or nerve substance, may be expected to be lacking.

Whether or not signs of local pressure are first apparent, the intracranial effusion, if it be of any magnitude, is bound to lead to a general increase of intracranial pressure. The signs of this condition are well known.

The most characteristic symptom in the presence of moderately raised pressure is headache, which is frequently accompanied by vomiting; a further increase leads to the addition of mental excitement and confusion; and a still greater rise produces a state of coma, which may lead to signs of medullary compression and death.

These signs of increased intracranial pressure would naturally be expected to vary, in a case of subarachnoid haemorrhage, with the character and extent of the leakage and with its subsequent course.

Thus there may be :

1. At one end of the scale a sudden large haemorrhage causing such immediate and gross increase of pressure as to lead to coma and death in a few hours.

2. The initial haemorrhage may be sudden and severe as above, but may be



checked. The patient will then pass from a state of coma into one of mental confusion with severe headache, and this may lead to recovery or death from a further attack.

3. A sudden *small* haemorrhage may give rise to the sudden onset of headache or vomiting; (a) this, if unchecked, will lead progressively to mental confusion, coma, and death; (b) or the haemorrhage may be checked, leading to recovery at any phase of the illness.

4. Slow leakage as from a vein will give rise to the gradual onset of headache and vomiting, and if progressive, lead through the stage of mental confusion to coma and death; or if non-progressive, may result in recovery at any of these stages.

These theoretical conclusions are borne out by clinical experience, and the pressure symptoms met with in subarachnoid haemorrhage are roughly divisible into these groups.

There are, however, two additional points of clinical observation which require explanation. One is the almost invariable occurrence from the sudden rupture of an artery, even if the subsequent extravasation be small, of a brief initial loss of consciousness. This is possibly due to the actual shock of rupture being equivalent to a sudden blow with resultant concussion.

The second point is the ability of certain patients after recovery to give an account of the actual experience of rupture, as that 'something seemed to snap at the base of my skull'.

This is doubtless due to the special sensibility of the meninges.

*B. Irritative effects.* Blood extravasated into the subarachnoid space acts as a foreign substance or irritant, and just as a haemothorax gives rise to the symptoms of pleurisy, subarachnoid haemorrhage gives rise to those of meningitis. In any case, therefore, of subarachnoid haemorrhage in which the extravasation is sufficiently extensive, the signs of meningitis—neck pain and stiffness, pains in the back and limbs, and Kernig's sign—may be expected, *provided that they are not masked by those of severe compression*. Together with these signs of meningeal irritation, there is a mild febrile reaction such as is usually met with when a quantity of extravasated blood is being broken up in, and absorbed by, a serous cavity.

Now, superimposing the signs of meningeal irritation upon those of cerebral compression, we may complete the clinical details of the classification already suggested as follows:

#### *Group I.*

The patient, being seized suddenly with severe headache and loss of consciousness, passes insensibly into a state of coma in which he dies.

This group, which is of little clinical interest, comprises a large number of cases in which the haemorrhage is derived from a wide arterial breach. Thus the majority of cases of intracranial aneurysm, and of atheromatous rupture, come under this heading. The patient is, as a rule, brought into hospital unconscious, and the diagnosis is made at autopsy.



The following cases exemplify the group :

*Ingvar, Obs. III, p. 324 (abstracted).* The patient, aged 53, had apparently been in good health, save for occasional headaches for the two days preceding the ictus to be described. He was then, while travelling in a motor-car, seized with violent headache and tinnitus, and became unconscious in a few minutes. At the onset some convulsive movements of one arm were observed. He was admitted to hospital in a state of coma and died in 48 hours. Autopsy revealed a ruptured aneurysm the size of a nut, situated upon the left middle cerebral artery close to its point of divergence from the internal carotid. The subdural and subarachnoid spaces were full of blood-clot, and this was especially abundant at the base of the brain and in the left temporal fossa. The kidneys and heart showed no gross abnormality.

*Froin, Obs. II, p. 64 (abstracted).* A man, aged 70, was admitted to hospital in a state of coma. From the history it appeared that this had begun with a stroke a few hours previously. On admission he was completely unconscious. No neck stiffness was present, nor Kernig's sign, but there was some general rigidity of the limbs. The urine (obtained by catheter) contained much albumin. Lumbar puncture yielded 2 c.c. of blood-stained fluid. In the test-tube the cells sank to the bottom without the appearance of a coagulum. Death occurred 24 hours after the onset.

At autopsy, extensive subarachnoid haemorrhage was disclosed. The arteries were extremely atheromatous. The exact source of the haemorrhage was not discovered. The heart was hypertrophied, the kidneys atrophied and cystic.

#### *Group II.*

The patient is seized suddenly with severe headache and loss of consciousness, passing insensibly into coma. From this he gradually recovers, with complaint of headache, vomiting, and symptoms of mental confusion. At this stage there may be observed signs of meningeal irritation and low pyrexia. This in turn may lead to complete recovery, or may be followed by a recurrence of stupor and coma (due to further leakage), and death.

In this group of cases, as recognized by Ehrenberg, the apoplectiform onset leads directly to a state of coma, and it is not until this passes off that the signs of meningeal irritation are unmasked. The sequence of events, as already outlined, is presumably as follows :

Following the initial concussion effect of the rupture, the rise of intracranial pressure is at first so rapid as to produce a lasting state of coma. As, however, the extravasated blood becomes diffused and at the same time clotting occurs, intracranial pressure is diminished, coma gives place to mental confusion, and the meningeal symptoms are revealed. The point of clinical distinction between the cases of this and the following group is that in this—Group II—the initial ictus is followed by a true state of coma resembling that of a commonplace cerebral haemorrhage, and the diagnosis in the early stages is therefore difficult.

The duration and depth of this state of coma are variable. Its importance lies in the fact that it is apt to mask meningeal symptoms. The relative rarity of cases in this group depends doubtless upon the fact that an effusion large enough to produce coma in the first instance usually proceeds unchecked to medullary compression without chance of recovery.

An example of this group is the following case:

*Conos and Xanthopoulos (17) (abstracted).* The patient, aged 38, had had syphilis and gonorrhoea. During coitus after a hard day's mental work, followed by a heavy meal, he suddenly vomited and lost consciousness. He remained in a semi-comatose state up till the time when he first came under the authors' observation two days later. He was then able to answer questions slowly and complained of headache. The temperature was subnormal, pulse 55. On the following day (the fourth day of his illness) he showed neck stiffness and Kernig's sign. He could be roused from his stuporous condition and answered questions in an intelligent manner. No signs of focal nervous lesion were discovered. Lumbar puncture gave 30 c.c. of a bright red fluid. Twelve hours later this had yielded a light deposit at the bottom of the tube, and the supernatant fluid appeared slightly pink. Microscopic examination showed abundant red cells. Following the lumbar puncture his condition improved. The complaint of headache was less, and the pulse-rate rose to 60. On the eighth day of his illness he was mentally clear, but the signs of meningeal irritation were still present. On the evening of this day the temperature was 100° F. and the pulse 75. A second lumbar puncture yielded 25 c.c. of fluid less heavily blood-stained than before. Microscopic examination showed an abundance of polynuclear cells. He gradually recovered.

### Group III.

The patient is seized suddenly with severe headache and brief loss of consciousness. Regaining his senses, he complains of headache and pain and stiffness in the back of the neck. The signs of meningeal irritation are found together with low fever. Subsequently either (a) headache continues to be the most severe symptom and is accompanied by vomiting: mental confusion supervenes and leads to coma and death; or (b) the signs of meningeal irritation remain predominant, being associated with more or less headache and mental confusion: these symptoms gradually pass away, and the patient recovers.

In this and the succeeding clinical group, as opposed to Groups I and II, persistent unconsciousness appears only as a late or terminal symptom in sub-group (a) of fatal issue. Meningeal symptoms are therefore revealed in the early stages—immediately after the initial ictus—and the condition of sub-arachnoid haemorrhage is rather apt to be confused with that of meningitis than with cerebral haemorrhage.

*Sub-group (a).* In the fatal cases the illness may be prolonged, sometimes with repeated apoplectiform seizures due to recurrent leakage, or the whole sequence of events may be compressed into a short space.

Examples of each variety are to be found in the following cases:

*Ehrenberg Case II (abstracted).* A woman of 57 had in 1906 a sudden attack of headache with unconsciousness, said to have lasted 24 hours. This was followed by severe headaches for several months. On December 18, 1911, she was seized suddenly with intense suboccipital headache, lost her senses, and remained unconscious for 20 minutes. On regaining consciousness she vomited. During the next 24 hours she had two similar attacks associated with jerking movements of the arms and dyspnoea.

Between these attacks she was conscious, complained of headache and stiffness of the neck, and frequently vomited. On December 20 she was somnolent.

The head was retracted, the neck stiff. The optic disks were normal; there were two recent retinal haemorrhages in the right fundus. The cranial nerves appeared normal. There was no loss of motor or sensory functions as far as could be determined. The plantar reflexes were indefinite. Kernig's sign was positive: the limbs could not be flexed past an angle of  $45^\circ$ . The blood-pressure was 220/145; the urine contained albumin. On December 22 temperature and pulse rose, she passed into a state of coma and died. At autopsy there was extensive basal subarachnoid haemorrhage. The actual source of the haemorrhage was not discovered. The heart was hypertrophied, and the vessels generally showed atheromatous changes. 'Hypernephromas' were found in both kidneys.

*Doubler and Marlow* (21). A negress, aged 32, was admitted to hospital on October 12, 1916, at 5 p.m. On account of her mental state a complete history could not be obtained. From her physician, who came to the hospital, it was learned that her family history was negative, her previous health good. At 1 p.m. on the day of her entrance she was suddenly seized, while at work, with vomiting and fainted. The vomiting soon ceased. She seemed to regain consciousness, but was unable to talk. No convulsion, paralysis, or facial asymmetry was noted.

On admission her pulse was 65, respirations 30, rectal temperature  $101.3^\circ\text{F}$ . Her heart was slightly enlarged, and a few extra-systoles were noted. Her neck was slightly stiff. Knee-jerk was absent on the right side, and on the left barely obtainable.

Achilles' tendon and plantar reflexes were absent on both sides. The arm reflexes were not observable because the patient resisted manipulation, and continuously made well-coordinated but purposeless motions with her arms. There was no evidence of paralysis. The pupils reacted to light. Eye movements were well performed. Kernig's sign was negative, and no ankle clonus was made out. In other respects the examination was negative.

A lumbar puncture showed a bloody fluid under considerable pressure, 30 c.c. being removed. The red cell count in this spinal fluid was 392,000 per c.mm. There was slight temporary improvement after lumbar puncture.

At the first ophthalmoscopic examination of the right eye a large red, apparently fresh haemorrhage was seen located on the disk, partly obscuring its upper half. There were a few smaller peripheral flame-shaped haemorrhages not impinging upon the disk or any blood-vessel. In the left eye the retinal veins were engorged. There were a few small haemorrhages scattered about. The picture was quite different from the right eye. Both fundi were examined from time to time. The large haemorrhage on the disk in the right eye grew in size till the disk was completely obscured. It partly filled the nasal side of the fundus, and appeared to be extending into the vitreous. At one examination it seemed as though the haemorrhage could be seen to undergo enlargement. The haemorrhages in the left eye changed very little.

The patient died at 11.20 p.m., 6 hours and 20 minutes after her admission. Wassermann reactions on both blood and spinal fluid were negative. Her blood-urea nitrogen was normal, Hb. 105; white cell count 25,000. Urine contained albumin, bacteria, a few red cells, no casts.

At the autopsy extensive subarachnoid haemorrhage was found, apparently originating from a small aneurysm of the left internal carotid. Other areas of thinning were found in this artery and its branches. The heart was somewhat hypertrophied; there were hyaline changes in the splenic vessels, and 'a slight degree of chronic nephritis'.

The details of further examination will be considered later in this paper in the section dealing with the ophthalmoscopic appearances.

*Sub-group (b).* The non-fatal cases of Group III form the large majority of all those cases which ultimately recover.

The following case, which I have reported in the Guy's Hospital Reports (65), is a characteristic example: A nursing sister, aged 52, had always enjoyed good health, with the exception of occasional headaches for the past few weeks. On April 24, 1922, she began to feel unwell at lunch and did not want to finish her meal. Feeling rather faint, she retired to her room, and then 'suddenly there was a whirling feeling at the base of my skull, and something seemed to snap'. The resident medical officer being called, found her in a semi-conscious state, and ordered her to bed.

She gradually regained her senses, but then complained of intense headache, at first frontal, then fronto-occipital, with pain in the back of the neck radiating 'down into the spine.' The temperature chart showed an irregular rise to about 100° F. Five days later she presented definite neck stiffness, and an occasional extensor plantar reflex on the left. She still had a slight rise of temperature, and the suspicion of meningitis was aroused.

Lumbar puncture on this occasion, and again three days later, yielded evenly blood-stained fluid.

She made a gradual recovery, and when last heard of was well save for occasional headaches. Her blood-pressure was—systolic 155, diastolic 70 mm. Hg.

#### *Group IV.*

This group has only a hypothetical existence. Venous oozing has been invoked to explain certain cases of subarachnoid haemorrhage (as will be mentioned later), but its occurrence has not yet been proved, and the claim to probability rests upon negative conclusions. It would be natural to suppose that in the case of gradual leakage from a vein the initial ictus would be lacking from the clinical picture, and that there would be a slow onset of headache, vomiting, pain and stiffness of the neck, and low fever.

3. *The ophthalmoscopic appearances in subarachnoid haemorrhage.* In the case of Doubler and Marlow already quoted, a striking feature was the occurrence of a large retinal haemorrhage in the right fundus, which increased in size under observation and appeared to be extending into the vitreous. Very similar appearances have been recorded by Hale-White (41) and myself (65) in subarachnoid haemorrhage due to ruptured aneurysm.

Hale-White's case was that of a labourer aged 21, who was found post-mortem to have a ruptured aneurysm of the right internal carotid just before its termination, but had presented no signs of disease during life up till the moment of the fatal illness. Except for the aneurysm and subarachnoid haemorrhage, the autopsy revealed no abnormality. 'All the other cerebral vessels were quite healthy, so were all the vessels in the rest of the body, every organ of which was perfectly healthy.'

The ophthalmoscopic appearances in this case were described by Hale-White as follows:

'There was no optic neuritis nor atrophy, but on the outer side of the right disk was a large prominent, dark brick-red subretinal swelling. This encroached a little on the disk, and was four times the size of it. It was thought to be subretinal haemorrhage. A similar swelling was seen in the left eye.'

The post-mortem note states: 'On removing the skull blood-clot was found

in both the subdural and subarachnoid cavities. It was all about the base of the brain, and there was a good deal on the upper surface. The haemorrhage had passed forwards in the sheath of the optic nerves, which were much distended with blood-clot, and ultimately tore its way forward under the retina.'

My own case (65) was that of a woman aged 52, with generalized arteriosclerotic changes and a ruptured aneurysm of the right internal carotid at its point of junction with the posterior communicating artery. Twenty-four hours before death the fundi in this case showed venous engorgement and blurring of both disks, a few punctate haemorrhages in both retinae, and on the left 'the edge of the disk was obscured by one of several large subretinal<sup>2</sup> accumulations of blood. It was noted at the time that these had not the ragged outline usually seen in large retinal haemorrhages.' At the autopsy, which revealed extensive subarachnoid haemorrhage, blood was found within the arachnoid sheaths of both optic nerves.

Here then are three clinical observations independently made of a somewhat unusual ophthalmoscopic appearance, in each case associated with the post-mortem discovery of a ruptured aneurysm of the internal carotid. The further investigation of the optic nerves and eyeballs by Doubler and Marlow in their case elucidates the pathology of the condition. Sections cut transversely and longitudinally showed the optic nerve sheaths to be greatly distended with blood, which had apparently forced its way forward through the lamina cribrosa, and ruptured in turn the retinal and hyaloid membranes.

The fact that in all these three cases the haemorrhage originated from an aneurysm of the internal carotid is probably not without significance, for both the situation of the artery and its size would favour a pressure of fluid blood in the optic nerve sheaths sufficient to force a passage through the lamina cribrosa.

As to the frequency with which subhyaloid extravasations may occur as a result of subarachnoid haemorrhage we can form no valid opinion, for in the majority of recorded instances of the latter condition there is no mention of the ophthalmoscopic appearances. It appears certain, however, that they are not constant, and that in cases which survive long enough other evidence of increased intracranial pressure may be revealed in the form of papilloedema and retinal haemorrhages.

Bramwell (13) and Mott and Stedman (51) have published instances of fatal subarachnoid haemorrhage from intracranial aneurysm in which papilloedema was observed during life, and microscopic sections showed the optic nerve sheaths to be distended with blood. Among the 124 cases of spontaneous subarachnoid haemorrhage which form the basis of the present review, there are 14 only in which special mention is made of the fundi. In two instances they are described as normal. In three cases (recorded above) there were subhyaloid haemorrhages. In three others there were 'two recent haemorrhages in one' (24), in another

<sup>2</sup> It has been pointed out to me by Mr. Goulden and Dr. Riddoch that both this description and that of Hale-White, already quoted, would apply rather to subhyaloid than subretinal haemorrhage. This also would accord with the observation by Doubler and Marlow of haemorrhages which subsequently appeared to be extending into the vitreous.



'extensive bilateral haemorrhages' (19), and in the other 'foyers d'hémorrhagies rétinéennes dans les deux yeux' (3). In the remaining 6 (10, 19, 24, 32, 65) the disks are described as swollen or blurred, without haemorrhages. In one of these cases (32), as in one other (43) in which the fundi were not examined, the onset of the attack was accompanied by sudden blindness, which in the latter led rapidly to death, whilst in the other vision slowly returned with recovery. In this case the disks were swollen, but no haemorrhages were observed.

4. *Massive albuminuria in subarachnoid haemorrhage.* The occurrence of transient 'massive albuminuria' in subarachnoid haemorrhage was first noted by Widal (73) in 1903. This was the case of a woman, aged 39, who was seized suddenly with headache, vomiting, and pain in the back of the neck. She was admitted to hospital on the fifth day of her illness in a stuporous condition with signs of meningeal irritation. Lumbar puncture revealed the characteristic picture in the cerebro-spinal fluid. On admission the urine contained 2 parts per 1,000 of albumin. As the clinical condition improved the albuminuria diminished and finally disappeared. Fifteen days after the original attack the patient had a further haemorrhage, of which she shortly died.

Post-mortem a ruptured aneurysm was discovered arising from the right middle cerebral artery. There was extensive subarachnoid haemorrhage and the ventricles also were full of blood. There were no degenerative changes in the vessels save at the actual point of origin of the aneurysm, where there was a line of atheroma. Microscopic examination revealed chronic endarteritis at this point. No mention is made of the state of the kidneys.

Commenting upon the transient albuminuria in this case, Widal remarked that both clinical and experimental evidence supported the notion that albuminuria might occur as the result of cerebral lesions, especially of the brain stem.

Guillain and Vincent (39), in 1909, recorded the case of a woman aged 54, who had a sudden attack of cerebral symptoms. On the second day of this illness lumbar puncture revealed subarachnoid haemorrhage, and the urine contained 20 parts per 1,000 of albumin. The blood-pressure at this time was 210 mm. Hg. After admission her condition improved, and she was able to leave the hospital after 9 days. By this time the urine was free from albumin.

Guillain and Vincent referred to similar instances in the literature, and considered that massive albuminuria might have some diagnostic value in cases of subarachnoid haemorrhage. Their views were embodied in the following year in Schneider's (62) thesis, in which the literature of albuminuria in association with nervous lesions is fully reviewed.

Schneider reminds his readers that Claude Bernard (8) in his classical experiments was able to produce albuminuria as well as glycosuria from lesions of the floor of the fourth ventricle. 'Quand on pique', dit-il, 'sur la ligne médiane du plancher du quatrième ventricule, exactement au milieu de l'espace compris entre l'origine des nerfs acoustiques et l'origine des nerfs pneumo-gastriques, on produit à la fois une exagération des deux sécrétions hépatique et rénale; si la piqure atteint un peu plus haut, on ne produit très souvent que



l'augmentation dans la quantité des urines qui sont alors souvent chargées de matières albuminoïdes.' And in another passage (9): 'Lorsque j'ai fait des piqûres de la moelle allongée, il m'est le plus souvent arrivé de produire le diabète, mais souvent aussi j'ai produit en même temps de l'albuminurie, quelquefois même l'albuminurie a existé seule. L'albuminurie peut donc passer dans les urines par suite d'un état particulier du système nerveux.'

Vulpian (71) later confirmed this observation, producing albuminuria from lesions of the fourth ventricle in dogs, and showed that albuminuria also resulted from section of the great splanchnic nerve in these animals.

The possibility of clinical albuminuria as a result of a nervous lesion therefore rests upon a sound basis of physiological experiment, and in addition many clinicians have recorded observations of albuminuria in cases of sudden and severe cerebral disturbance, such as apoplexy and epilepsy.

Schneider adds to the list of cases in which 'massive albuminuria' has been associated with subarachnoid haemorrhage one personal observation, and four others from the literature. He lays stress upon the presence of a large quantity of albumin, without casts or blood, occurring at or immediately after the onset of the haemorrhage, and showing a tendency to rapid and progressive diminution. In his own case on the day of onset there were 30 parts per 1,000, which had diminished to a trace on the tenth day. Subarachnoid haemorrhage was diagnosed from lumbar puncture. There was a second attack in which the patient died, but no autopsy was allowed.

In the case reported by Gerest and Lafond (34) there were 5 parts per 1,000 on the second day, a trace only on the ninth. The patient, who was known to be a chronic nephritic, recovered.

In Chauffard's (15) case there were 9 parts per 1,000 on the first day with subsequent disappearance. At autopsy ventricular and subarachnoid haemorrhage.

In one of Froin's (32) cases (a chronic nephritic) there had been 3-4 parts per 1,000 for some time before the ictus, which then increased to 9 parts per 1,000. Death was due to a cerebral haemorrhage which had burst into the lateral ventricles. In another of Froin's (32) cases there were 9 parts per 1,000 on the first day, and on the fifth day a trace only. In this patient also a chronic nephritic death was again due to a cerebral haemorrhage which had ruptured into the ventricles.

Unfortunately in no one of the cases which have been mentioned was the absence of renal disease clearly established on clinical or post-mortem evidence.

On the other hand, there is positive evidence of renal disease in the majority.

The case least open to suspicion of renal disease as a cause of the albuminuria is that of Widai (73) in which the cause of subarachnoid haemorrhage was an aneurysm, but, as already related, there is no mention of the state of the kidneys at autopsy.

Schneider, following Guillain, regards 'massive albuminuria' when present as a valuable aid to diagnosis in obscure cases of subarachnoid haemorrhage.

Neither Ehrenberg nor Ingvar refer to the point. Goldflam, however, mentions one case in which the urine contained 5 parts per 1,000 of albumin, and also casts and pus cells. The patient recovered and the urine became normal.

In summary of the literature upon this point it may be said that transient 'massive' albuminuria is a rare accompaniment of spontaneous subarachnoid haemorrhage; there is good physiological evidence for supposing that this albuminuria may be due to disturbance of nervous centres concerned with renal secretion; but at present proof is lacking that the symptom may occur solely as the result of subarachnoid haemorrhage in a person with healthy kidneys.

### *Pathological.*

The known pathological causes of spontaneous subarachnoid haemorrhage are those which lead to haemorrhage elsewhere in the body. Of these the commonest is arterial degeneration of the type generally known as arterio-sclerosis, a condition usually associated with cardiac and often with renal disease, and which is probably of toxic or infective origin. This condition may lead to direct rupture of an artery or to the formation of an aneurysm with subsequent rupture.

Other causal agents of the toxi-infective group are the acute bacterial infections of haemorrhagic type (among which anthrax (60, 66) appears predominantly as a cause of meningeal haemorrhage), chronic alcoholism, and syphilis, which, like arterio-sclerosis, may lead to rupture of an artery either directly or through the formation of an aneurysm.

Aneurysms of other origin which may lead to subarachnoid haemorrhage are those which result from infective endocarditis and embolism, and the group already referred to in which the aneurysm is unassociated with other arterial disease and depends upon a local defect of the media, possibly of congenital origin.

Haemorrhage into the subarachnoid space may also occur in diseases of the blood, in thrombosis of the superior longitudinal sinus, in eclampsia, and in sunstroke, or from the walls of tumour or cyst.

Of the 124 cases which I have collected from the literature it appears that in 71 the haemorrhage was due to one of the above causes.

*Arterio-sclerosis* was responsible in 29 of these, as witnessed by specific mention of clinical or post-mortem evidence of arterial disease, cardiac hypertrophy, or renal disease. Of these 29 cases, 25 proved fatal. The age incidence in this group is, as might be expected, relatively high. In 27 instances in which the age is stated the youngest patient was 32, the oldest 88, with an average age incidence of 57.

In the fatal cases the actual source of the haemorrhage was discovered in only 4 out of the 24 examinations. This on the whole is not surprising, for the search for a small rent in an extracerebral artery amongst a diffuse mass of blood-clot is in itself a laborious and uncertain process, and the probability is

that an aperture sufficiently large to produce a fatal haemorrhage may after death, when the vessel walls are shrunken, be invisible to the naked eye.

Closely allied to the preceding group in point of pathology is that of 11 cases in which the patient was known to be suffering from *chronic alcoholism*, the cause here again being a toxic degeneration of vessel walls. Of this group 7 died and 4 recovered. In the fatal cases the post-mortem records are incomplete. It is possible that in some of them the cause of haemorrhage may have been a terminal infection of haemorrhagic type.

*Syphilis* was the primary cause in 10 cases, of whom 5 died and 5 recovered. In 9 of these cases there was clinical or serological evidence of syphilis, and in the other microscopic examination of the pial vessels after death revealed changes which were considered characteristic of the disease.

Syphilis must therefore be considered a relatively frequent cause of spontaneous subarachnoid haemorrhage, although, contrary to former belief, it has been shown to be a rare cause of intracranial aneurysm.

The nature of the pathological process in these cases has been summarized by Turnbull (69) as follows:

'When the smaller muscular and elastic arteries are the seat of syphilitic inflammation, endarteritis is usually a marked figure, the lumen becoming almost obliterated. It is clear that in such a condition aneurysmal dilatation is excluded. In some cases of intense inflammation with necrosis the adventitia and media become greatly weakened before the intima has greatly thickened; in such cases aneurysmal dilatation might occur, but in my experience such intense inflammation has led to rupture or false aneurysm and not to true aneurysm.'

In 11 cases in this series, all fatal, the cause was a *ruptured aneurysm*. They are included here because they have come to my notice in a search through the literature of subarachnoid haemorrhage and therefore presumably attracted notice as examples of this condition. Whereas the literature of subarachnoid haemorrhage is scanty, that of intracranial aneurysm is relatively abundant. Beadles (5) in 1907 was able to collect 555 cases, including 114 of his own. Fearnside (29) in 1916 added 44 new cases to the literature, and many other instances have doubtless been published.

The relative frequency of a leaking intracranial aneurysm as a cause of subarachnoid haemorrhage is not accurately known. The discovery of an aneurysm at autopsy is doubtless more likely to be recorded in the journals than a case of subarachnoid haemorrhage without any discernible source. On the other hand, intracranial aneurysm is not uncommon. Fearnside found that in a series of 5,432 post-mortem examinations of the head at the London Hospital between 1907 and 1913 intracranial aneurysms were discovered in 44 cases, or in 0.80 per cent., and that in the *total* number of 7,924 necropsies made during the same period, rupture of a cerebral aneurysm led to death in 0.44 per cent., whilst direct rupture of an intracranial artery during the same period was the cause of death in 0.91 per cent., i.e. that the frequency of intracranial aneurysm as a cause of death is about half that of cerebral and meningeal haemorrhage.

Moreover, it is admitted by all observers that leakage from an intracranial

aneurysm is a recoverable condition, and that multiple seizures at considerable intervals of time may precede the fatal haemorrhage.

When we add to these considerations the fact that a ruptured aneurysm upon the surface of the brain may be so minute and so deeply imbedded in blood-clot as readily to be missed, and observe further that in the majority of the reported cases of subarachnoid haemorrhage with recovery there is no record of the subsequent history, we are I think entitled to conclude that aneurysm is probably a commoner cause of subarachnoid haemorrhage than has hitherto been supposed.

Of the 11 cases in this series in which autopsy proved a ruptured aneurysm to have been the cause of subarachnoid haemorrhage, one was that of an aneurysm of the descending aorta, the haemorrhage having spread upwards intrathecally. The remainder were instances of intracranial aneurysm. In three there were signs of generalized arterio-sclerosis, in one the cause was infective endocarditis, another occurred in a subject of syphilis. In one I have been unable to gain access to the complete data, whilst in four instances it is recorded that the patient had not suffered from syphilis, there was no history of alcoholism, and no evidence of generalized arterial degeneration.

The ages of the last four patients were 32, 36, 39, and 41.

The occurrence of spontaneous subarachnoid haemorrhage in *sunstroke* has been the subject of a paper by Dufour (22). His case was that of a Customs official aged 26, who, after prolonged exposure to an excessively hot sun, collapsed suddenly and was admitted to hospital unconscious, with signs of meningeal irritation. Serial lumbar punctures revealed the characteristic picture of subarachnoid haemorrhage. Dufour refers to other observations upon abnormalities of the cerebro-spinal fluid in *sunstroke*, but quotes no other case of frank haemorrhage.

Bouquet's (11) case was that of a child of 14 with acute onset of meningeal symptoms after exposure to the sun and bloody cerebro-spinal fluid. I have not seen the original paper.

Both these patients recovered.

I have included also in this group one of Froin's cases (*Obs. VIII*, p. 99). In that the patient, a man of 36 in good health, received his ictus while riding in a carriage after a meal on August 31 'par une température très élevée'. He also made a complete recovery.

Other writers (46) have remarked upon symptoms of meningeal irritation in *sunstroke*, but without changes in the cerebro-spinal fluid other than an increase of pressure and raised cell count.

It is known that in fatal cases of heat hyperpyrexia intense congestion may be observed of the surface of the brain and the meninges, and that petechial haemorrhages may occur in the skin and mucous membranes. Some severe, but non-fatal, cases present sequels which indicate permanent cerebral damage; this has been attributed to haemorrhage.

Willcox (77), however, in an account of heatstroke in Mesopotamia records

that 'lumbar puncture was performed on several cases; the cerebro-spinal fluid was clear and sterile, and the pressure was above normal'.

The evidence, therefore, which I have been able to collect in favour of sunstroke or heatstroke being a true cause of spontaneous subarachnoid haemorrhage is scanty, and the possibility must be kept in mind that the heat to which these patients were subjected was but a precipitating cause of leakage from an aneurysm or damaged vessel.

*Tumours and cysts* of the brain would appear to be an infrequent cause of subarachnoid haemorrhage. There are two cases in my series. One patient (43), aged 24, had had ten years before an attack of meningo-encephalitis, which left him subject to attacks of Jacksonian epilepsy. Death was sudden with loss of consciousness passing into coma. At autopsy an old cyst was found, which was thought to be a relic of the past infection. A vessel in the wall of this had apparently ruptured directly into one of the lateral ventricles.

The other case as reported by Gintrac appears to have been one of traumatic cyst formation following head injury, with eventual rupture of a vessel in its wall.

The remaining cases in which an adequate cause for the haemorrhage was discovered post-mortem need no comment. They were: two cases of *thrombosis of the superior longitudinal sinus* in patients aged  $1\frac{1}{2}$  and 80 (35), one case of *pernicious anaemia* (76), one case of *haemophilia* (50), one case of *eclampsia* (35).

There are then left 53 cases of the total of 124 in which the cause of the haemorrhage appears obscure. In several of these the obscurity is probably due to faulty or incomplete pathological diagnosis.

Thus in six cases (four of cerebral, two of spinal (27, 35) subarachnoid haemorrhage), of whom one only was below the age of 60, no mention is made of the state of the arteries, and it is reasonable to suppose that the haemorrhage in these cases was due to arterial degeneration.

In another case (59) the haemorrhage is said to have originated from rupture of the left anterior cerebral in a man of 50, probably also an instance of arterio-sclerotic degeneration.

In a further group of four cases from Gintrac's collection, mostly recorded before the introduction of the clinical thermometer, the clinical and post-mortem data suggest the probability of a haemorrhagic infection. And in one of Wilks's (75) cases the patient was in hospital for post-puerperal endocarditis at the time of her fatal seizure, which makes it possible that she may have had an undetected aneurysm of embolic origin.

There remain 41 cases in which *the pathological cause of the haemorrhage was obscure*. Eighteen of these cases died and came to autopsy without revealing any adequate cause for the subarachnoid extravasation.

Of 39 cases in this group in which the age is available, the range is from 10 to 58, with an average of 30. Thus both in its age incidence and in its mortality rate this group presents a striking contrast to the largest group of known causation—the arterio-sclerotic cases.



Many writers have commented upon the obscurity of the pathological cause of haemorrhage in this group of cases. Ehrenberg and Ingvar admit the difficulty.

Bittorf (10), reporting a typical case in a young man of 24 with recovery, argues that the cause was a subacute haemorrhagic leptomeningitis. His arguments, however, are based upon imperfect conclusions, for he takes as evidence of infection the fever, and the association with the blood in the cerebro-spinal fluid of an excess of polymorphs. As it is known that both these phenomena may occur in cases of simple subarachnoid haemorrhage, as from a non-infective aneurysm, the validity of Bittorf's hypothesis cannot be admitted. It may further be urged that an infection severe enough to produce extensive meningeal haemorrhage is not likely to lead to recovery, and that this in itself renders the theory of a haemorrhagic leptomeningitis improbable as an explanation of Bittorf's and other cases.

Another hypothesis has recently been put forward by Goldflam (36) in explanation of certain of the obscure cases of subarachnoid haemorrhage. He notes, as others have done, that many of the patients attacked are young persons in normal health at the time of onset. Taking this into conjunction with the negative post-mortem appearances in certain fatal cases, he suggests that the cause may be a functional disturbance of vasomotor control analogous to that which is said to occur in migraine, Raynaud's disease, and erythromelalgia. His thesis appears to be that, in the stage of active hyperaemia which follows that of abnormal vaso-constriction, capillary oozing may take place upon the surface of the brain. In support of his view he refers to 13 cases of subarachnoid haemorrhage personally observed, of whom no less than five suffered from true migraine. Unfortunately no detailed account of these cases is given, which largely detracts from the value of the paper. Goldflam also appears to be unaware of the 'congenital' group of aneurysms, for he rules out the possibility of aneurysm in ten of his cases on the ground that they were all under 30 years of age and presented no signs of vascular disease.

In the series of obscure cases at present under discussion I have searched carefully for a history of migraine, but have met with a suggestive history in two cases only, both reported by Gintrac. One was a boy of 14, apprentice to a painter, who was 'sujet aux maux de tête'; the other a man of 40 'sujet aux congestions cérébrales légères'. Both terminated fatally, and in both a large subarachnoid haemorrhage was found with no discernible cause.

Whatever may be the association of migraine with spontaneous subarachnoid haemorrhage, Goldflam's hypothesis of capillary oozing is, I think, open to objection. For the brusque manner of onset in these cases is inconsistent with such a gradual process as he describes. Moreover, our knowledge of the pathology of migraine is still far from complete, and we are hardly justified in assuming, for the purpose of further argument, that it depends upon vasomotor disturbance.

I have already given my reasons for believing that intracranial aneurysms



are a commoner cause of spontaneous subarachnoid haemorrhage in young people than is generally supposed. And in this connexion it is interesting to compare the age incidence of the group of cases under discussion with that of Fearnside's (29) group of fifteen cases of intracranial aneurysm, which in virtue of the absence of any other signs of cardiac or vascular disease were considered to be due to congenital defect in the media. In the present group of forty-one cases the average age is 30, in Fearnside's fifteen cases the average age was 38. The correspondence on the whole is close.

To sum up the arguments in favour of my view, they are that :

1. Intracranial aneurysms in young persons with no signs of cardio-vascular disease are of relatively common occurrence.
2. Such aneurysms may give rise to the symptoms of subarachnoid haemorrhage from leakage with recovery, and months or years may elapse before further leakage occurs.
3. Thus in the case of a young person who recovers from a subarachnoid haemorrhage the true diagnosis of intracranial aneurysm is frequently missed, if the case be not carefully followed.
4. In the event of such an aneurysm causing death, the age of the patient and the absence of cardio-vascular changes may often divert suspicion from the true cause, and the aneurysm, being frequently minute and always deeply embedded in blood-clot, therefore escapes notice.

Whether these aneurysms in young and apparently healthy persons are indeed due to congenital defects, or whether they are caused by a local infective or degenerative process, is a matter for further inquiry, and this raises the further question whether some of the obscure cases of spontaneous subarachnoid haemorrhage may not be due to direct rupture of an arterial branch from local softening without the formation of an aneurysm. That such an event may result from syphilitic arteritis seems clear, and there are possibly similar infective processes yet unrecognized. A local lesion of this kind would lie hidden in the masses of blood-clot even more surely than an aneurysm, and would probably escape detection unless the meningeal vessels were washed free of clot and systematically examined with a lens.

#### *Differential Diagnosis.*

This question has been much discussed in the literature, which however calls for no detailed review in this paper. A proper examination of the cerebro-spinal fluid suffices to establish the diagnosis of subarachnoid haemorrhage, when the clinical evidence is doubtful.

The difficulty in certain cases—belonging to Groups I and II of my clinical classification—is the differentiation of primary subarachnoid haemorrhage from cerebro-meningeal haemorrhage, in which the blood-stained cerebro-spinal fluid originates from an intracerebral haemorrhage which has ruptured internally into

one of the ventricles or externally into the subarachnoid space. In the cases of Group I the distinction cannot be made save at autopsy.

In the cases of Group II the differential diagnosis depends upon the absence in cases of primary subarachnoid haemorrhage, of signs of a gross intracerebral lesion, for certainly an intracranial haemorrhage sufficiently large to rupture into the ventricles or subarachnoid space would give rise to permanent cerebral damage (if indeed any such case ever recovers).

In the cases of Groups III and IV the distinction has to be made from meningitis, but the examination of the cerebro-spinal fluid is sufficient criterion.

#### *Treatment.*

The question of practical importance under this heading is under what circumstances lumbar puncture should be employed as a therapeutic measure.

By some authorities (16) repeated drainage by this route is recommended without reserve. In some recorded cases, however, death has immediately followed this procedure from fresh haemorrhage from the aneurysm, doubtless provoked by the sudden diminution of external pressure upon the vessel wall, when a quantity of fluid is withdrawn from the subarachnoid space.

Both Ehrenberg and Ingvar therefore advise a cautious attitude, and the latter, reflecting upon a disastrous experience of his own, has summarized the position as follows:

In subarachnoid haemorrhage there are two stages to be observed. The first is that in which haemorrhage is actively proceeding. In this stage the increased intracranial pressure occasioned by the extravasation has a protective value in tending to reduce the rate of leakage and so promote coagulation.

In this stage therefore, though it may be necessary to remove a small amount of fluid for diagnosis, therapeutic puncture is contra-indicated, with one very important exception. The danger to life in this early stage of subarachnoid haemorrhage is lest the effusion cause fatal increase of intracranial pressure. In such circumstances the risk of death from compression outweighs that of the operation itself, and lumbar puncture with drainage may offer the only opportunity of saving life.

In the early stages of subarachnoid haemorrhage, therefore, the indications for therapeutic puncture are the signs of a dangerous increase of intracranial pressure, especially if these be progressing.

In the second stage of subarachnoid haemorrhage, after the haemorrhage has ceased, the phenomena of meningeal reaction are predominant. These, as has already been stated, are due to the irritative effect of the extravasation upon the cerebral and spinal meninges, which induces an increased secretion of cerebro-spinal fluid together with an increase in the formation of white cells. The condition, as Ingvar points out, is analogous to that which may result from the intrathecal injection of a foreign serum. In this stage the headache and pains

may undoubtedly be relieved by repeated lumbar punctures. The operation should, however, be practised with caution. The patient should be in the lying posture, a manometer should be used, and the pressure of the cerebro-spinal fluid should not be allowed to fall below 100 mm.

These arguments and the conclusions drawn from them appear to be sound.

The value of therapeutic puncture must be a matter for judgement in the individual case, guided by the principles which Ingvar has set forth.

Eskuchen (26) has proposed, and put into practice, the injection of gelatin intrathecally in the acute stage with the object of promoting coagulation. In the case which he reports this procedure was undertaken four times in the course of a week. From 10 to 25 c.c. of cerebro-spinal fluid were removed at each puncture, and from 5 to 15 c.c. of 10 per cent. gelatin subsequently injected. Following the last injection of gelatin the patient, who had up till that time been improving, had an attack of right-sided Jacksonian epilepsy followed by paresis of the right arm and face with aphasia. He finally made an incomplete recovery.

This remedy would appear to be of doubtful value, and not without risk of further damage.

*Cases of Spontaneous Subarachnoid Haemorrhage now reported for the First Time.*

*Case I. Subarachnoid haemorrhage in a man of 47, the subject of chronic nephritis; death nine months later from cerebral haemorrhage.*

A labourer, aged 47, having previously enjoyed good health, had a sudden seizure with loss of consciousness. He was admitted a few days later (the history is incomplete) with the tentative diagnosis of encephalitis lethargica. He was then noted to be 'very drowsy, speaks incoherently, plantar reflexes flexor, knee-jerks present, pupils react normally'.

On the day following admission the notes state that he was very drowsy, but would answer questions with his eyes half closed. There was apparent weakness of both sixth nerves, but no other physical signs.

Cerebro-spinal fluid obtained the same day was examined by Dr. Perdrau, who reported as follows:

Fluid clear and brownish, no clotting on standing.

Total protein 0.1 per cent., sugar less than normal.

Chlorides 0.68 per cent., cells 69 per c.mm., and 15 R.B.C. per c.mm.  
Differential count of whites:

95 per cent. lymphocytes;

5 per cent. polymorphs;

No plasma cells.

Spectroscopic examination showed two absorption bands of a haemoglobin derivative.

On the following day I found that he was conscious but drowsy with sighing respiration. There were no signs of local destruction of the central nervous system. He showed, however, definite neck stiffness, and a positive Kernig's sign. Ophthalmoscopic examination revealed neuro-retinitis of the typical albuminuric appearance, together with one very large haemorrhage near the left optic disk, and a few small haemorrhages in the right fundus. The systolic

blood-pressure was 190, and the urine contained a trace of albumin. The Wassermann reaction in the blood was negative.

The patient made a gradual but uninterrupted recovery, and left the hospital after two months in apparently good health. His systolic blood-pressure at that time was 210 mm. Hg.

On discharge he resumed work for a month, but was unable to keep it up owing to general debility. Nine months later he was readmitted, having been struck down with apoplexy in the street. He was found on admission to be comatose with a right hemiplegia, and died within twenty-four hours.

The autopsy revealed a recent large haemorrhage occupying the greater part of the left hemisphere. No signs of any previous cerebral haemorrhage were discovered. The arteries at the base of the brain were not carefully examined. The kidneys showed the characteristic changes of chronic Bright's disease.

I conclude that in this case the original illness was due to rupture of some small vessel at the base of the brain with subsequent healing.

This case is a good example of what must be a not uncommon accident in cerebral arterio-sclerosis. We were fortunate in being able to demonstrate later at post-mortem the absence of any old-standing cerebral haemorrhage, which makes it certain that the original effusion was derived from a superficial vessel.

The cerebro-spinal fluid showed a characteristic picture, and in its clinical features the case conforms with Group II of my classification.

*Case II. Fatal subarachnoid haemorrhage from aneurysm in a man of 24.*

A man, aged 24, was brought to hospital by the police and died a few hours after admission. He was in a state of coma when first seen, and is stated to have had epileptiform convulsions while under observation. No previous history was available. Just before death he appears to have had a small amount of sugar in his urine. The provisional clinical diagnosis made was status epilepticus. At the post-mortem there was abundance of blood in the subarachnoid spaces at the base of the brain, with extension upwards into the Sylvian fissures and the neighbouring sulci. The rest of the bodily organs were those of a healthy young man. The diagnosis suggested was that in the course of an epileptic convulsion one of the cerebral veins had given way under the increased pressure.

The brain was preserved as an example of meningeal haemorrhage. Subsequent dissection revealed a small thin-walled aneurysm at the first point of bifurcation of the right anterior cerebral (Plate 4). The aneurysm lies actually in the apex of the Y formed by the two branches, which both appear to take origin from it. Its free wall, which is of the thickness of a sheet of notepaper, has ruptured.

Here then is a case in which the cause of a fatal meningeal haemorrhage might have remained obscure had not the aneurysm been carefully looked for. The remarks of Sir William Gull (40) written in 1859 are pertinent in this connexion.

As to its clinical features this case falls into Group I of my classification. In its causation it corresponds with that group of cases in which the aneurysm has been suspected of being due to a congenital defect in the vessel wall. Microscopic sections across the aneurysm in this case showed that at its point of origin not only is the media defective, but the intima is grossly hypertrophied. Moreover the intimal proliferation extends lengthwise down the artery to a point beyond that at which the media ceases to be defective.

Professor Turnbull, who has kindly examined these sections with me, and compared them with some of his own with which they show a close correspondence, considers that the intimal proliferation in these cases is secondary to the medial defect.

The microscopic picture on the whole, however, closely resembles that of an acquired arterio-sclerotic lesion, and, although the other arteries of the brain both to the naked eye and on section appear normal, I am of opinion that the

possibility should still be considered that this aneurysm represents the result of an acquired local lesion of toxic or infective origin.

*Case III. A man, aged 37, having for 26 years been subject to attacks both of epilepsy and migraine, but otherwise in good health, had an attack of subarachnoid haemorrhage from which he made a complete recovery.*

The patient had since the age of 11 suffered from attacks which he described as being of two different varieties.

The one variety was clearly of an epileptic nature. There was an aura of pins and needles and twitching, sometimes commencing in the hand, sometimes in the foot, but always on the left side. This was followed by clonic spasms of the left arm and leg, proceeding to generalized convulsions with loss of consciousness.

The other variety of attack he described as follows:

He would perhaps be walking in the street when he would become aware of what he called 'a spot' obscuring his vision on the left side. This spot looked to him like an irregular watery patch always on the move, which gradually increased in size until his whole vision appeared blurred, as if he were looking through a mist. At the same time he sometimes experienced a feeling of pins and needles in the left hand, face, and foot. There was never any nausea, vomiting, or headache. He did not lose consciousness and was able to carry on with his work as long as this did not involve reading, for which his vision became too dim. The whole attack would last a few minutes.

These attacks, he said, had no relation whatever to the epileptic attacks, and did not alternate with them.

On May 30, 1923, he had a typical epileptic attack in a cinema. During the following week he felt poorly, and complained of a muddled head, but continued at work. On June 6 he played tennis for three hours. At 7 p.m. he went into his garage and cranked up his car. He then came out complaining of a severe pain in the back of the neck. His wife noticed a little twitching of the left hand and foot, and expected him to have one of his usual fits. Instead of this he continued to complain of severe headache and pain in the back of the neck, and vomited. The pain and vomiting continued for 24 hours, and his medical man administered morphia. He remained in bed for ten days, and on getting about again complained of pain in the bottom of the back. This was shortly followed by a recurrence of the headache, vomiting, and neck pain. Lumbar puncture was performed by his medical attendant, and a pinkish fluid was said to have been withdrawn which contained no organisms.

As his condition did not improve he was sent into Guy's Hospital two days later. On admission he was semi-conscious, his temperature was 100° F., he presented head retraction and Kernig's sign, but no other abnormal signs.

Lumbar puncture yielded fluid containing blood. In the tube was a considerable sediment of red cells; there was no clot; the supernatant fluid was yellow and gave a negative response with Van den Bergh's direct reaction, and a positive result with the indirect test (the reaction for altered blood pigment).

The protein was 0.09 per cent. The Wassermann was negative in blood and spinal fluid.

He gradually recovered, and when seen six months later was in good health. He has had several migrainous attacks lately, but no attack of epilepsy since his acute illness.

The clinical features of this case place it in Group III of my classification. Its pathology is obscure. The association with a long history of migraine and epilepsy is remarkable, and if there is any sound basis for Goldflam's hypothesis that subarachnoid haemorrhage in such cases may be due to vasomotor disturbance, here is a case which might be taken in support of his theories.



*Summary.*

1. A study of the literature shows that spontaneous (as opposed to traumatic) subarachnoid haemorrhage has engaged the attention of different observers chiefly (1) on account of its clinical symptoms and the state of the cerebro-spinal fluid obtained by lumbar puncture; (2) as a terminal event in intracranial aneurysm.

2. The anatomical pathways by which blood may gain access to the subarachnoid space are discussed, and primary subarachnoid haemorrhage differentiated from that secondary to subdural and intracerebral haemorrhage.

3. The clinical manifestations of subarachnoid haemorrhage are discussed under the headings of:

- (1) Cerebro-spinal fluid,
- (2) Symptoms and signs,
- (3) Ophthalmoscopic appearances,
- (4) Transient massive albuminuria,

with accounts of illustrative cases under each heading. An attempt is made at classification into four clinical groups upon a physiological and pathological basis.

4. The pathological causes of primary spontaneous subarachnoid haemorrhage are reviewed in 124 cases collected from the literature.

5. In 41 of these cases, with an average age incidence of 30, no satisfactory cause was found.

6. Some hypotheses which have been put forward in explanation of these obscure cases of spontaneous subarachnoid haemorrhage are criticized, and it is suggested that in some of these cases the haemorrhage may have originated from undiscovered aneurysms of the type not uncommon in young people, and supposed to be due to a congenital defect in the media.

7. The differential diagnosis and treatment of spontaneous subarachnoid haemorrhage are briefly discussed.

8. Three new cases are reported and reviewed in the light of previous considerations.

I am much indebted to Dr. A. H. Douthwaite, formerly Chief Clinical Assistant in the Neurological Department, Guy's Hospital, for his help in abstracting the German literature.

## BIBLIOGRAPHY.

1. Achard and Paiseau, *Gaz. des hôp.*, Paris, 1904, 498.
2. Babinski and Jumentié, *Bull. et mém. Soc. méd. des hôp. de Paris*, 1912, 3<sup>e</sup> sér., xxxiii. 858.
3. Baréty and Thaon, *Nice médical*, 1877, v. 171 (quoted by Schneider).
4. Bauer, *Arch. gén. de méd.*, Paris, 1903, ii. 3026.



5. Beadles, *Brain*, Lond., 1907, xxx. 285.
6. Bernard, *Réunion méd.-chirurg. de la X<sup>e</sup> Armée* (Sect. Sud), May 25, 1915 (abstr. *Rev. neurol.*, Paris, 1916, xxx. 652).
7. Bernard, Ch., quoted by Ehrenberg from Vigneras.
8. Bernard, Claude, *Leçons de physiol. expériment. appliq. à la méd.*, Paris, 1855, l. 839.
9. Bernard, Claude, *Leçons sur les propriétés phys. et les lésions path. des diff. liquides de l'organisme*, Paris, 1856, ii. 137.
10. Bittorf, *Deutsch. Zeitsch. f. Nervenheilkunde*, Leipz., 1915-16, liv. 375.
11. Bouquet, *Province méd.*, 1908, 398 (abstr. *Rev. neurol.*, Paris, 1909, xvii. 1386).
12. Brailion, *Gaz. des hôp.*, Paris, 1909, lxxxii. 635.
13. Bramwell, *Edinb. Med. Journ.*, 1886, xxxii. 97.
14. Charles et Denis, *Journ. de méd. de Bordeaux*, 1905 (quoted by Schneider).
15. Chauffard, *Journ. de méd. et de clin. prat.*, Paris, 1903, 717 (quoted by Schneider).
16. Collier, J. S., *A Textbook of the Practice of Medicine by Various Authors*, edited by Price, Lond., 1922, 1351.
17. Conos et Xanthopoulos, *L'Encéphale*, Paris, 1912, i. 18.
18. Courmont et Cade, *Arch. de neurol.*, Paris, 1900 (quoted by Schneider).
19. Cushing, *Guy's Hosp. Reports*, Lond., 1923, lxxiii. 159.
20. Déjerine, *Rev. neurol.*, Paris, 1908, xvi. 706.
21. Doubler and Marlow, *Arch. Ophthal.*, New York, 1917, xli. 533.
22. Dufour, *Rev. neurol.*, Paris, 1909, xvii. 317.
23. Durand, *Thèse de Lyon*, 1902, 74 (quoted by Schneider).
24. Ehrenberg, *Hygieia*, 1912, lxxiv. 849.
25. Eppinger, *Arch. f. klin. Chirurg.*, Berlin, 1887, 35, Supplement, p. 1 (quoted by Fearnside).
26. Eskuchen, *Zeitsch. f. d. ges. Neurol. u. Psychiat.*, Berlin, 1919, xlvii. 331.
27. Etienne, *Rev. méd. de l'Est*, Nancy, 1909, xli. 414.
28. Fallot, *Arch. gén. de méd.*, Paris, 1830, xxiv. 438.
29. Fearnside, *Brain*, Lond., 1916, xxxix. 224.
30. Follet et Chevrel, *Gaz. des hôp.*, Paris, 1910, 547 (quoted by Ehrenberg).
31. Forssheim, *Deutsch. Zeitsch. f. Nervenheilk.*, Leipz., 1913, xlix. 123.
32. Froin, 'Les hémorragies sous-arachnoïdiennes et le mécanisme de l'hématolyse en général', *Thèse de Paris*, 1904.
33. Gaillard et Boyé, *Bull. et mém. Soc. méd. des hôp. de Paris*, 1909, 1268.
34. Gerest et Lafond, *Loire méd.*, 1910, xxix. 117 (quoted by Schneider).
35. Gintrac, *Maladies de l'appareil nerveux*, Paris, 1869-71, i. 649.
36. Goldflam, *Deutsch. Zeitsch. f. Nervenheilk.*, Leipz., 1923, lxxvi. 158.
37. Griolier, *Progrès méd.*, Paris, 1912, xl. 46.
38. Guillaumin, *Presse méd.*, Paris, 1915, xxiv. 441.
39. Guillaumin et Vincent, *Sem. méd.*, Paris, 1909, 505.
40. Gull, *Guy's Hosp. Rep.*, Lond., 1859, 3rd ser., v. 281.
41. Hale-White, *Trans. Clin. Soc.*, Lond., 1895, xxviii. 5.
42. Hayem, *Hémorragies intrarachidiennes*, *Thèse de l'Agrégation*, Paris, 1872.
43. Ingvar, *Nouv. icon. de la Salpêtrière*, Paris, 1916-18, xxviii. 313.
44. Launois et Mauban, *Arch. gén. de méd.*, 1903, ii. 1561.
45. Letulle et Lemièrre, *Bull. et mém. Soc. méd. des hôp. de Paris*, 1904, 3<sup>e</sup> sér., xxi. 1121.
46. Lian, *Presse méd.*, Paris, 1915, xxiii. 354.
47. Macris, *Presse méd.*, Paris, 1915, xxiii. 379.
48. Médecin, *Thèse de Paris*, 1910 (quoted by Schneider).
49. Meylahn, *Deutsch. Zeitsch. f. Nervenheilk.*, Leipz., 1923, lxxviii. 78.
50. Moizard et Bacaloglu, *Bull. et mém. de la Soc. anat. de Paris*, 1900, lxxv. 969 (quoted by Ehrenberg).
51. Mott and Stedman, *Lancet*, Lond., 1889, ii. 15.
52. Netter et Clerc, *Bull. et mém. Soc. méd. des hôp. de Paris*, 1900, 967.
53. Ollivier, *Traité des mal. de la moelle épinière*, 1837, ii. 112 (quoted in extenso by Hayem, 42).

54. Orticoni, *Réunion méd.-chirurg. de la X<sup>e</sup> Armée*, 1915 (Sect. Sud), (abstr. *Rev. neurol.*, Paris, 1916, xxx. 652).
55. Perrin, *Rev. méd. de l'Est*, Nancy, 1907, xxxix. 243.
56. Pfeufer, *Zeitsch. f. ration. Med.*, Zurich, 1844, i. 293.
57. Poisot et Vincent, *Arch. gén. de méd.*, 1900, l. 376.
58. Porot, *Rev. de méd.*, Paris, 1908, xxviii. 38.
59. Richon, Hanns, et Fairise, *Soc. de méd. de Nancy*, 1913 (abstr. *Rev. neurol.*, Paris, 1913, xxvi. 692).
60. Risel, *Zeitsch. f. Hyg. u. Infektionskrankh.*, Leipz., 1903, xlii. 381 (quoted by Teacher).
61. Roy et Levy, *Bull. et mém. Soc. méd. des hôp. de Paris*, 1910, xxix. 842.
62. Schneider, *Les albuminuries des hémorragies méning.*, Thèse de Paris, 1910.
63. Sergent et Grenet, *Loire méd.*, 1908 (quoted by Ingvar).
64. Siredey, Lemaire, et Denis, *Bull. et mém. Soc. méd. des hôp. de Paris*, 1914, xxxviii. 247.
65. Symonds, C. P., *Guy's Hosp. Rep.*, Lond., 1923, lxxiii. 139.
66. Teacher, J. H., *Lancet*, Lond., 1906, l. 1306.
67. Tezeras du Montcel, *Loire méd.*, 1909, xxviii. 621 (abstr. *Rev. neurol.*, Paris, 1910, xix. 414).
68. Turnbull, *Brain*, Lond., 1918, xli. 50.
69. Turnbull, *Quart. Journ. Med.*, Oxford, 1914-15, viii. 201.
70. Vigneras, *Thèse de Paris*, 1908 (quoted by Ehrenberg).
71. Vulpian, *Recherches expériment.*, *Mém. de la Soc. de biol.*, Paris, 1861 (quoted by Schneider).
72. Wichern, *Deutsch. Zeitsch. f. Nervenheilk.*, Leipz., 1912, xlv. 220.
73. Widal, *Presse méd.*, Paris, 1903, ii. 413.
74. Widal et Merklen, *Bull. et mém. Soc. méd. des hôp. de Paris*, 1899, xvi. 899.
75. Wilks, *Diseases of the Nervous System*, 2nd edit., Lond., 1883, 107.
76. Wilks, *Guy's Hosp. Rep.*, Lond., 1859, 3rd ser., v. 119.
77. Willcox, *Trans. Med. Soc.*, Lond., 1920, xliii. 207.

## DESCRIPTION OF PLATE.

PLATE 4. Showing subarachnoid haemorrhage from a small aneurysm at the bifurcation of the anterior cerebral artery. The patient was aged 24. The other cerebral vessels were healthy. No signs of disease were discovered elsewhere.



W.  
THORNTON  
SHIELDS



## CHOLESTEROL IN THE BLOOD IN CASES OF GALL-STONES

By J. M. H. CAMPBELL<sup>1</sup>

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### 1. *The Aetiology of Gall-stones.*

WITH increasing knowledge of bacteriology the older view that gall-stones were formed by stagnation of the bile was gradually replaced by the belief that they were mainly due to inflammation within the walls or cavity of the gall-bladder.

Infection was first suggested as their cause by Galippe in 1886, and soon after *B. coli* and staphylococci, and later *B. typhosus*, were found in gall-stones. Bernheim had remarked on the close association between typhoid and gall-stones, and it was shown that *B. typhosus* might still be in the gall-bladder many years after the original attack of typhoid (1). Gilbert and others found *B. coli* in a large proportion of stones, and by introducing it experimentally into the gall-bladder succeeded in setting up cholecystitis, which resulted in the formation of stones (1).

Nauyn showed that in the absence of a catarrhal condition of the walls the introduction of foreign bodies, or even of gall-stones, into the bladder did not result in calculus formation (3). This was confirmed by a very careful series of experiments by Harley and Barratt (2). In five dogs the gall-bladder was opened and gall-stones were introduced aseptically. Six months or a year later the dogs were killed, and in no case could any trace of stones be found. In six other dogs gall-stones and pus were introduced, and six months or a year later they were killed. In four which were still infected the gall-stones were unchanged, and in two, where the sepsis was less, the stones were smaller but had not disappeared. This proves that in the absence of sepsis the dog's bile is able to redissolve even large calculi. It is by no means true that in the absence of sepsis human gall-stones are always redissolved, though this may happen sometimes.

For these reasons and others, the view that all gall-stones are inflammatory in origin has been widely accepted by the writers of most modern text-books,

<sup>1</sup> Beit Memorial Research Fellow. Most of the experimental part of this work was done during the tenure of the Hilda and Ronald Poulton Fellowship at Guy's Hospital.

though other predisposing causes are recognized. Among these may be mentioned stagnation of the bile due to changes in abdominal pressure, and diets containing a large amount of cholesterol. Nauyn (3) supposed that cholesterol was not excreted by the liver, but that it came from the gall-bladder and bile ducts, especially when they were inflamed. There is now a good deal of evidence against this.

The other view of the origin of gall-stones, which has been advocated warmly by Chauffard (21), is that stones are formed when there is an excess of cholesterol to be excreted in the bile. If any chemical change is responsible it is likely to be concerned with cholesterol metabolism, as that is the main constituent of most human gall-stones. Large stones of calcium bilirubinate occur in oxen, but when such stones occur in man they are nearly always small. An analogous case to this view of Chauffard's would be the pigment stones which occur so frequently in acholuric jaundice when there is an excess of pigment to be excreted.

Under what conditions may an excess of cholesterol appear in the bile? It occurs normally in the blood in fairly constant amounts, both free and combined as ester (12). After feeding on meat, eggs, or other foods rich in cholesterol, the amount is considerably raised (7, 19), and it is also increased in pregnancy and various pathological conditions. McNee (8) has shown that the amount of cholesterol in the bile is high at the same time as in the blood. The same end result would be reached if the bile became less capable of holding it in solution. One older view supposed that on a vegetable diet there was a smaller production of bile salt and a diminished power of the bile to hold cholesterol in solution.

It has been recognized for a long time that gall-stones occur more frequently in women, and most frequently in women who have borne children. In view of the increased cholesterol in the blood and in the bile during the later months of pregnancy it seemed possible that the changes in cholesterol metabolism might be the cause of the frequency of gall-stones in women. This view has been warmly supported by Chauffard. Even if it is correct some other factor must be involved in the production of gall-stones, for there is an equally large amount of cholesterol in the blood in cases of diabetes and some types of nephritis, and there is no tendency for gall-stones to be associated with these diseases.

From quite a different point of view Aschoff has opposed the view of the inflammatory origin of all gall-stones (4). He found that in the large solitary cholesterol stone there was frequently no evidence of infection, and supposed that the stone had been formed aseptically. But apart from the direct experimental method of producing stones by infection, the indirect bacteriological methods are rather inconclusive, because bacteria may pass right into a gall-stone which was previously sterile, just as they pass through a coarse filter.

In the same way it is probable that all traces of an infection may die out, and this may have happened in Aschoff's cases. Some recent work of Howell and Knott's supports this view (26). In most of the cases of this series, when the gall-bladder was removed, they examined the contents of the bladder and the



stone itself. In a large proportion both were sterile. The wall of the gall-bladder was also examined histologically, and there was rarely any evidence of recent inflammation, though there was generally fibrosis, probably from an old infection which had died out.

Dewey (10) has recorded some interesting experiments. He found that gall-stones could be produced in rabbits by feeding with cholesterol. The stones were sterile and the gall-bladder showed no signs of inflammation. Other pathological changes were produced in the liver and in the kidneys, but, curiously enough, none of the rabbits developed arterio-sclerosis. The experiments are opposed to those of Harley and Barratt in dogs, but it is more than likely that different groups of animals react differently to cholesterol. It may explain why gall-stones are never found in wild carnivorous animals, while they occur frequently in the domestic herbivorous animals.

## 2. *Cholesterol in the Blood in Cases of Gall-stones.*

Chauffard and some others claim that in most, if not all, cases of gall-stones the amount of cholesterol in the blood is increased above normal. Were this proved, and were the blood in other abdominal conditions shown to be normal, it would provide strong evidence that the amount of cholesterol in the blood, and therefore in the bile, was an important factor in the production of gall-stones.

This had been investigated by several workers, as it is obviously of considerable importance for diagnosis and for treatment, when it is remembered that a diet rich in cholesterol can increase considerably the amount in the blood. Henes found that it was constantly increased in cases of gall-stones (9). Chauffard in his excellent work on gall-stones (21) says, 'Je crois donc que l'on est autorisé à dire que dans la règle les cholélithiasiques sont des hypercholestérinémiques, et cela non seulement pendant les périodes d'ictère par rétention, mais même alors qu'ils ne sont que peu ou pas subictériques'.

Flandin (22), examining 29 cases of Chauffard's, found that in all but two the cholesterol in the blood was more than 0.2 per cent., and in ten it was between 0.3 and 0.55 per cent. (These lower values are not much higher than the normal found by Bloor (11), but they must be compared with the normal found by the same method, 0.16.) In a recent text-book a table of significant changes in the blood includes the cholesterol values in cholelithiasis as from normal to 0.3 per cent., from the results of Rothschild and Rosenthal (24).

This would seem ample to establish an increase of cholesterol in the blood as a probable cause of gall-stones were it not for a large number of negative results. Dennis (13) and Gorham and Myers (14) found that there was no constant increase, and Reimann and Meigon (15) and Schnabel (18) came to the conclusion that it was frequently just as high in other abdominal conditions and that the determination was not of much value. Unfortunately the digitonin method has not been applied to the problem. The most convincing results are those of

Myers (17). The method was carefully controlled, and the cases of gall-stones were part of a long series of various pathological conditions. The findings in these agreed with what has been found by others using the digitonin method, and in the case of gall-stones he found quite normal figures.

In view of this discrepancy it seemed worth while reinvestigating the question. At the same time as the author Bell started work on the problem at Leeds, using an almost identical method. In spite of this we have reached opposite conclusions about the value of the determination (25). It seems unlikely that this could be due to the very slight difference of method, but until his results are published more fully they cannot be properly discussed. It is possible that many of the high values which have been obtained depend on the presence of jaundice, due to the gall-stones, at the time when the blood was examined. The quotation from Chauffard rather suggests that this was so in many of his cases. In a recent paper by Wilensky and Rothschild (28) this was certainly true of many of their cases, though not of all.

### 3. *Methods of Investigation.*

The most reliable way of estimating cholesterol is the digitonin method of Windaus (5), but for clinical purposes it is not easy, as it requires a large amount of blood. Bloor and Knudson (12), McNee (8), and Gardiner (20) have shown that comparable, though not quite so accurate, figures can be obtained by the colorimetric method. This makes use of the colour reaction produced by adding acetic anhydride and strong sulphuric acid. It was worked out by Grigaut (6), and the actual technique used here was suggested by Myers and Wardell (16), and recently described in full in this Journal by MacAdam and Shiskin (23). The only change is that a larger proportion of sulphuric acid—0.5 c.c. instead of 0.1 c.c.—has been added, because Gardiner (20), after a prolonged examination of various methods, states that this is the most satisfactory. With these proportions the colour develops almost at once, and reaches its maximum in ten minutes at room temperature in ordinary light. Apart from this change the method used by Bell was identical (25).

Exact details will be found in these papers (16, 23), but shortly the method was as follows: 1 c.c. of plasma was mixed with 4 gm. of anhydrous plaster of Paris and heated in an oven for an hour at 70–80° C. The dry paste was then ground up and extracted with 20 c.c. of chloroform for one hour on an electric heater. The extract was made up to 20 c.c. and filtered. Five c.c. of the filtrate were mixed with 2 c.c. acetic anhydride and 0.5 c.c. concentrated sulphuric acid, and the resulting colour was compared with a standard solution of cholesterol to which the same reagents had been added. The green colour was not a very easy one to match, and more consistent results were obtained by electric light. In spite of every care to use clean and dry vessels and to avoid over-heating, a brown colour was mixed with the green in a certain number of experiments.

# CHOLESTEROL IN THE BLOOD IN CASES OF GALL-STONES 127

This always gave readings which were much too low, and they have been discarded.

To test the accuracy of the method, solutions of cholesterol in chloroform of various strengths were made up and estimated after going through the usual routine. In three cases out of fifteen the error was more than 10 per cent., but in no case was it more than 20 per cent. The average result was 7 per cent. above or below the true value.

Approximately the same error was found when blood of unknown cholesterol content was estimated independently by two observers. The results are shown in Table I.

TABLE I. *Degree of Accuracy to be expected in Colorimetric Determination of Cholesterol.*

Actual Cholesterol. mg. per 100 c.c.	Cholesterol found. J. M. H. C. mg. per 100 c.c.	Cholesterol found. A. J. McN. mg. per 100 c.c.	Percentage error. J. H. M. C.	Percentage error. A. J. McN.
100	104	104	+4	+4
120	122	98	+2	+18
140	162	134	+16	+4
160	148	154	-8	-3
180	188	—	+5	—
200	190	—	-5	—
—	132	144	+6	—
—	158	152	-4	—
—	170	156	-8	—
—	206	212	+3	—
—	216	182	-16	—

The method cannot be described as very accurate, but the changes in some pathological conditions are so great that it is still of use. Probably the error with some workers is less than this, but to me the green was often hard to match even when precautions were taken to avoid the development of the brown colour which has been a difficulty to many (16, 20, 23).

It was suggested that the chloroform extraction was less efficient than extraction with alcohol and ether after precipitating the protein. Little difference was found in a case of anaemia, the figures being 113 mg. per 100 c.c. by the usual method, and 126 after alcohol and ether extraction. It was also suggested that one hour's extraction with chloroform was not sufficient, but on one blood the usual method gave 167, six hours' extraction gave 156, and twelve hours' gave 184, changes which are hardly significant considering the experimental error.

On many occasions close agreement was found between separate determinations, e.g. one normal blood was found to contain 152 mg. cholesterol, 170 mg. after ten days, and 165 a month later. Plasma was used for all determinations unless otherwise stated, but as a rule no great difference was found between plasma and whole blood; e.g. in one woman the plasma value was 106 and the corpuscle value was 103, and the figure for whole blood was 114.

4. *Results of this Investigation.*

The blood of 52 subjects was examined, and many of these on more than one occasion. After this it seemed clear that there was no change in the cholesterol content in cases of gall-stones, so the investigation was not continued. In this series were 22 patients in whom disease of the gall-bladder was diagnosed. In ten the presence of gall-stones was confirmed by operation, and in six a diagnosis of gall-stones was made on clinical evidence and no operation was performed.

Of the remaining six, in three a laparotomy showed inflammation of the gall-bladder and no stone, and in three a diagnosis of cholecystitis was made on clinical evidence.

The general results are shown in Table II, and full details of each case are given in Table III.

TABLE II. *Cholesterol in the Blood in various Pathological Conditions, mainly of the Gall-bladder.*

Diagnosis.	Number of Subjects.	Cholesterol in the Blood in mg. per 100 c.c.	
		Average.	Range.
Gall-stones proved by operation	10	133	110-170
Gall-stones diagnosed on clinical evidence	6	130	113-150
Cholecystitis	6	143	118-162
Various abdominal conditions with no evidence of gall-bladder disease	8	132	98-192
Normal controls	12	153	107-191
Various conditions: jaundice, pregnancy, and diabetes	6	233	170-450
Anaemia	4	104	83-120

Apart from conditions like pregnancy, jaundice, and diabetes, where the increased amount of cholesterol in the blood is generally recognized, the highest values were actually found in normal subjects, but the difference was not sufficient for any significance to be attached to it. It may be that the normal figures were really higher because the subjects were all getting about in good health or as out-patients, while the others were in bed on a ward diet.

The rest in bed and the low diet cannot be responsible for any great reduction in the figures, for in the other conditions where high cholesterol figures have been reported they were found in each case; e.g. three subjects with jaundice gave values of 192, 203, and 450; two who were respectively seven and eight months pregnant, 170 and 194; and one with diabetes mellitus, 192 mg. per 100 c.c. It is quite clear that the method used was sufficiently accurate to show the high values found in pregnancy, jaundice, and diabetes, and the low values found in various types of anaemia.

In the two cases of acholuric jaundice examined the amount of cholesterol in the blood was increased after splenectomy, as was found by MacAdam and Shiskin (23).

# CHOLESTEROL IN THE BLOOD IN CASES OF GALL-STONES 129

TABLE III. *Cholesterol in the Blood in various Pathological Conditions, mainly of the Gall-bladder.*

Serial Number.	Original Diagnosis.	Result found at Operation.	Sex.	Cholesterol Content of Plasma.
8	Gall-stones	Three small stones in cystic duct	m.	183
5	Gall-stones	Stones in gall-bladder	f.	150
7	Gall-stones	Stones in gall-bladder	m.	184
9	Gall-stones	Stones in common bile-duct	f.	186
17	Gall-stones	Numerous small stones in gall-bladder	f.	110
18	Gall-stones	Stones in gall-bladder	m.	115
21	Gall-stones and slight jaundice	One large gall-stone and mucocele of gall-bladder	m.	152
27	Gall-stones	Three stones in common bile-duct	f.	150
45	Gall-stones	Two gall-stones; fibrotic bladder	f.	122
48	Gall-stones	Stones in gall-bladder	f.	170
2	? Recurrence of gall-stones	—	m.	185
20	? Gall-stones	—	m.	187
30	Gall-stones	—	m.	119
41	? Gall-stones	—	f.	118
46	? Gall-stones	—	f.	113
47	Gall-stones	—	m.	150
16	Cholecystitis	Chronic inflammation, no stones	f.	162
29	Cholecystitis	—	f.	125
32	Cholecystitis after pregnancy	Chronic inflammation, no stones	f.	140
37	Cholecystitis	—	m.	118
44	? Cholecystitis	—	m.	138
50	Cholecystitis	Chronic inflammation, no stones	f.	175
1	Gall-stones	Appendix removed; gall-bladder normal	f.	192
6	Gall-stones	Chronic appendicitis; gall-bladder normal	m.	123
10	? Gall-stones	Appendix kinked; gall-bladder normal; adhesions round duodenum	f.	98
15	? Gall-stones	Gall-bladder normal	f.	118
28	? Spinal caries	—	f.	141
39	Gastric ulcer	—	f.	158
43	Dyspepsia	Gall-bladder normal	m.	120
53	? Cholecystitis	Appendix removed; gall-bladder normal	f.	109
4	Mitral stenosis	—	f.	107
13	Normal, Oct. 1922	—	m.	152
14	Normal, Nov. 1922	—	m.	170
22	Normal, Dec. 1922	—	m.	167
23	Normal	—	f.	106
24	Normal	—	f.	171
25	Normal	—	f.	168
26	Neurasthenia	—	f.	166
34	Neuritis	—	f.	191
35	Neurasthenia	—	m.	105
36	Tabes dorsalis	—	m.	168
49	Facial paralysis	—	f.	180
11	Pernicious anaemia	—	f.	112
31	Secondary anaemia	—	f.	120
51	Acholic jaundice	—	f.	83
52	Acholic jaundice	—	f.	100
40	Sheep's blood	—	—	120
8	Jaundice	Chronic pancreatitis causing obstruction	f.	192
12	Jaundice, ? cause	—	m.	203
33	Jaundice (persistent)	—	m.	450
19	Pregnancy, 7 months	—	f.	170
38	Pregnancy, 8 months	—	f.	205
42	Diabetes mellitus	—	m.	192

### 5. *Summary and Discussion.*

The amount of cholesterol in the blood in cases of gall-stones and cholecystitis is within normal limits, provided the subject is not jaundiced. There is no evidence that the formation of gall-stones is caused by a raised cholesterol content of the blood and bile. It may be that in all the cases examined the active pathological change was over and the gall-stone was left as a legacy, but the normal findings in some cases of cholecystitis make this unlikely.

Some histological and bacteriological examinations of the gall-bladder in these cases by *Bowell and Knott* (26) suggest that the active inflammatory process was over and only fibrotic changes remained, when their symptoms brought the patients under observation for gall-stones.

The experimental evidence shows that in animals gall-stones can be produced by infections, and that in the absence of infection, in dogs at any rate, gall-stones will actually disappear if introduced. The only experimental evidence in favour of the view that increased cholesterol in the bile may cause gall-stones has been produced in rabbits. As feeding these animals with cholesterol readily produces arterio-sclerosis, and as this has not happened with other animals, it is not safe to draw conclusions about the production of gall-stones in men from experiments on rabbits.

The high cholesterol content of the blood and bile in pregnancy might be the explanation of the well-known incidence of gall-stones in women who have borne children. But the absence of gall-stones in cases of diabetes and arterio-sclerosis where there is as much or more cholesterol in the blood means that some other factor is involved. The mechanical changes produced in the abdominal cavity by pregnancy are probably the most important factors in predisposing to cholecystitis which may be followed by gall-stones, as they are in the production of pyelitis.

### 6. *Conclusions.*

1. The amount of cholesterol in the blood in cases of gall-stones and cholecystitis is within normal limits, provided the subject is not jaundiced. The determination is therefore of no help in the diagnosis of gall-stones.

2. This investigation lends no support to the theory that the formation of gall-stones is caused by a raised cholesterol content of the blood and bile. It does not exclude the possibility, for it may be that in all the cases examined the active pathological change was over and the gall-stone was left as a legacy. The normal findings in some cases of cholecystitis make this unlikely.

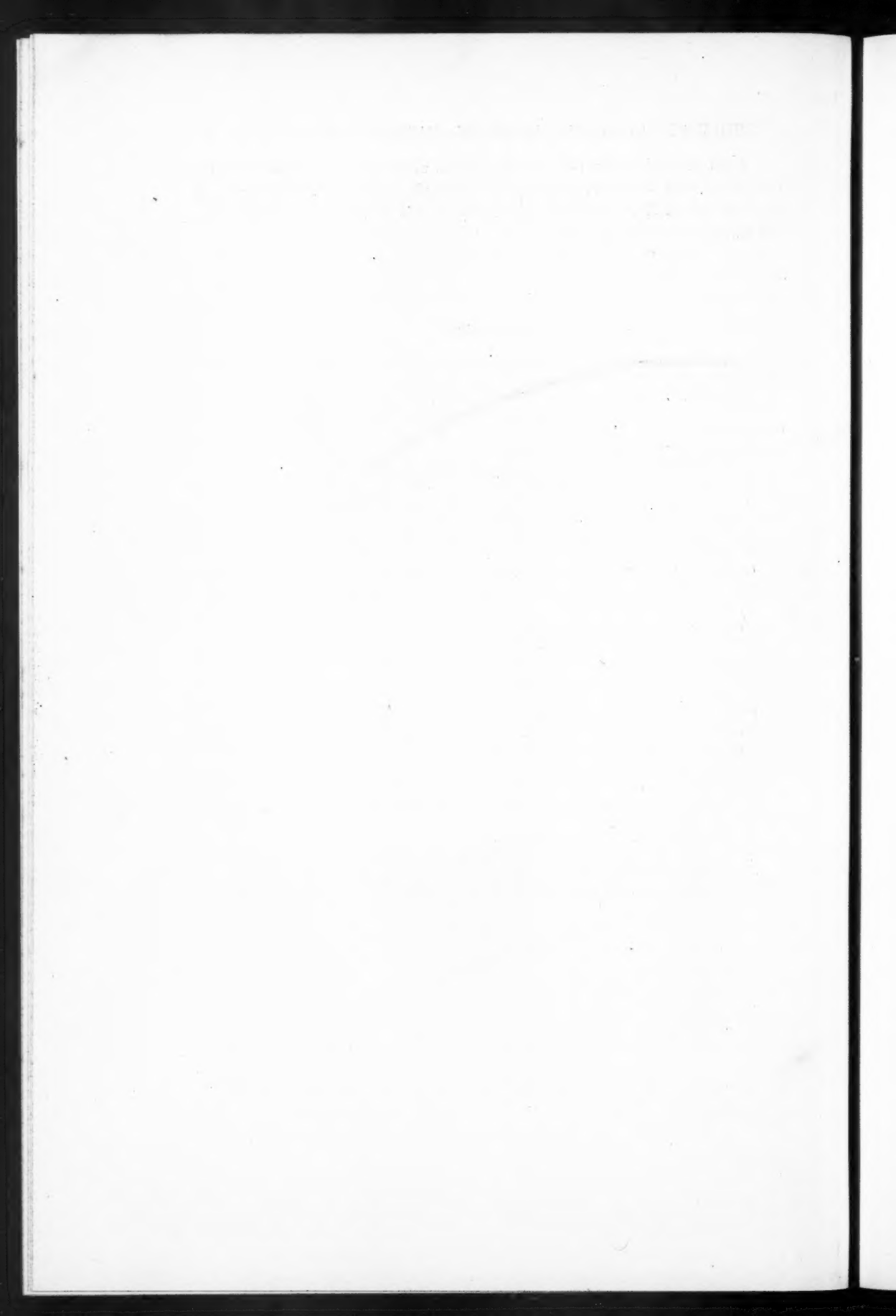
I wish to thank Dr. Hurst for suggesting the determination of cholesterol in the blood in cases of gall-stones, and for the opportunity of examining so many of his patients at Guy's Hospital and at New Lodge Clinic.



I am grateful to Dr. Bell for suggestions about the method of estimating cholesterol, and for showing me the results which he had obtained up to the time he returned to Australia, especially as his conclusions differed from my own.

# REFERENCES.

1. Various authors quoted by Mayo Robson, article 'Gall-stones', Allbutt and Rolleston's *System of Medicine* (second edition), 1914, vol. iv, part i, 254.
2. Harley, V., and Barratt, W., *Journ. of Physiol.*, 1903, xxix. 341.
3. Nauyn, quoted by Sir A. E. Garrod, article 'Hepatic Disease', Pembrey and Ritchie's *General Pathology*, Lond., 1913, 635.
4. Aschoff, *Münch. med. Woch.*, 1913, 60.
5. Windaus, *Ber. der Deutsch. chem. Gesellsch.*, 1909, xlii. 238.
6. Grigaut, *Comptes rendus Soc. Biol.*, 1910, lxviii. 791.
7. Gardiner, J. A., and Ellis, *Proc. Roy. Soc.*, 1912, B. lxxxv. 392.
8. McNee, J. W., *Quart. Journ. Med.*, 1914, vii. 221.
9. Henes, *Journ. Amer. Med. Ass.*, 1914, lxiii. 146.
10. Dewey, K., *Arch. Int. Med.*, 1916, xvii. 784.
11. Bloor, W. R., *Journ. Biol. Chem.*, 1916, xxv. 577 and 596.
12. Bloor, W. R., and Knudson, A., *ibid.*, 1916, xxvii. 107, and 1916, xxix. 7.
13. Denis, *ibid.*, 1916, xxiv. 229.
14. Gorham and Myers, *Arch. Int. Med.*, 1917, xx. 4.
15. Reimann and Meigon, *Surg., Gynaecol., and Obstet.*, 1918, 282.
16. Myers and Wardell, *Journ. Biol. Chem.*, 1918, xxxvi. 147.
17. Myers, V. C., *Journ. Lab. and Clin. Med.*, 1920, v. 776.
18. Schnabel, T. G., *Amer. Journ. Med. Sci.*, 1920, clx. 423.
19. Gardiner, J. A., and Fox, F. W., *Proc. Roy. Soc.*, 1921, B. xcii. 358.
20. Gardiner, J. A., and Williams, M., *Biochem. Journ.*, 1921, xv. 363.
21. Chauffard, A., *La Lithiase biliaire*, Paris, 1922, 43.
22. Flandin, quoted by Chauffard (21).
23. MacAdam, W., and Shiskin, C., *Quart. Journ. Med.*, 1922, xvi. 193.
24. Rothschild and Rosenthal, quoted by J. J. R. Macleod, *Physiol. and Biochem. in Modern Medicine* (4th edit.), 1923, 568.
25. Bell, J. R., *Brit. Med. Journ.*, 1924, i. 35.
26. Bowell, E. W., and Knott, F. A., *Guy's Hosp. Rep.*, 1924, lxxiv, 256.
27. Rous, P., McMaster, P. D., and Drury, D. R., *Journ. Exp. Med.*, 1924, xxxix. 77.
28. Wilensky, A. O., and Rothschild, M. A., *Amer. Journ. Med. Sci.*, 1924, clxviii. 66.



## SOME FACTORS OF SIGNIFICANCE IN ADOLESCENT GOITRE<sup>1</sup>

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### *Introduction.*

It is often a matter of difficulty to estimate the significance of a goitre in adolescence. Many instances are undoubtedly physiological, and disappear in a few years. Others, however, seem to be accompanied by signs of ill health, which may be attributed to disturbed thyroid function. From the point of view of treatment, it appears advisable to draw some distinction between these, and, in our opinion, the routine examination which we have adopted has enabled us to do this.

Our observations have been carried out on a series of 100 cases, of ages varying from 10 to 20. The chief points which we have investigated have been: (1) the physical measurements, height and weight, of these patients and comparison of these with the average normal standards; (2) the menstruation; (3) the basal metabolism; (4) the sugar tolerance.

### *Review of Pathology.*

To explain the subsequent classification of our cases, it is advisable to state briefly the modern views of the pathology of goitre. This has recently been done by Marine (1). There are three common groups of non-malignant goitre: (a) colloid; (b) hyperplastic; and (c) adenomatous; though transitional forms may occur. In all these, varying degrees of thyroid activity may be present. The majority of goitres in adolescence are of the colloid variety, though frequently different degrees of hyper- or hypoplasia are suggested by the clinical manifestations. These, however, are not so evident as in adults.

There seems to be general agreement as to the changes which take place in the formation of these goitres, though agreement is not universal as to the factors which initiate these changes. It appears that greater or lesser degrees of hyperplasia are produced and are usually followed by greater or lesser degrees of hypoplasia. If the exciting cause is especially severe, or active over a long period, the degree of hyperplasia may be advanced. In the milder cases

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however, after a period of activity, the gland usually reverts to the colloid or resting state. When this happens, the functions of the gland again become more or less normal, although it is increased in size; and although per unit of space its functional activity is diminished, this diminution is usually compensated for by the enlargement of the gland.

*Classification of Cases.*

The varieties in a series of cases such as ours would undoubtedly vary considerably with the neighbourhood from which they were drawn, for where goitre is endemic a large proportion of the cases would be of this variety. The present series of cases have been taken almost entirely from the London area, where goitre is not endemic; hence the few examples of endemic goitre. We have classified our cases into the following four clinical groups:

- |                                |                |                                 |
|--------------------------------|----------------|---------------------------------|
| I. <i>Colloid goitres</i>      | . 79 per cent. | A. Normal function 42 per cent. |
|                                |                | B. Hyperfunction 32 per cent.   |
|                                |                | C. Hypofunction 26 per cent.    |
| II. <i>Exophthalmic goitre</i> | 16 per cent.   |                                 |
| III. <i>Adenomata</i>          | . 3 per cent.  |                                 |
| IV. <i>Endemic goitre</i>      | . 2 per cent.  |                                 |

79 per cent. of the series fall into Group I, and of these thyroid function appears normal in 42 per cent. These comprise Sub-group A. In 32 per cent. there appears to be some degree of hyperthyroidism (Sub-group B), while in 26 per cent. there is some degree of hypothyroidism (Sub-group C). Of the remaining 21 per cent. of the series, 16 per cent. fall into Group II and are cases of adolescent exophthalmic goitre, differing in no way from cases of this condition seen in adults, excepting in the lesser severity of their symptoms; while in 3 per cent. the goitres were definitely adenomatous (Group III), and in 2 per cent. a history of endemic goitre could be obtained (Group IV). The number of cases falling into Groups III and IV are so few that it does not seem justifiable to draw any conclusions from our observations on them, so that the subsequent remarks apply entirely to the cases of Groups I and II.

*Comparison of Physical Measurements with Normal Standards.*

In making these comparisons the normal standards for age used are those described by Holt (2) for British children (Standards of Nutrition). Our measurements have been taken in bare feet and without clothes.

*Height.* It is well known that the thyroid gland exerts a profound influence on growth and development, and one of the most conspicuous consequences of thyroid deficiency in early life is the dwarfing of the individual. In examining the present series of cases of colloid goitre, the striking feature appeared to be that very many of our patients were overgrown and above the average height

# SOME FACTORS OF SIGNIFICANCE IN ADOLESCENT GOITRE 135

for their age. This is well seen in Table I, which shows the percentage number of cases differing from the normal standards of height.

TABLE I.

*Percentage number of Cases differing from Normal Standards of Height.*

Group I. Colloid Goitres.			
	Sub-group A. Normal Function.	Sub-group B. Hyperfunction.	Sub-group C. Hypofunction.
cm.	%	%	%
+ 10	9	12	20
+ 5	36	40	70
- 5	12	4	5
-10	0	0	0

It is obvious from this table that a large majority of these individuals are above the average standards of height for age. In fact, the percentage number below the average standards is negligible. Whether the increase in height above the average is the result of thyroid hyperactivity, or whether a goitre is especially liable to occur in overgrown individuals, is a question that cannot yet be decided; it is a point which requires further observation, and may have some bearing on what is usually termed the constitutional factor in these cases. We are at the present time investigating a possible pituitary factor in these individuals, which we hope may throw further light on this question.

In the above table it will be noticed that the highest percentage of those above the average height occurs in Sub-group C, but this may be accounted for by the assumption that these cases have already passed through a period of hyperactivity and are consequently of the longest duration.

*Weight.* The results of comparison of the weights of our series of cases of colloid goitre with the average standards for age are included in Table II, which shows the percentage of cases differing from the normal standards.

TABLE II.

*Percentage number of Cases differing from Normal Standards of Weight.*

Group I. Colloid Goitres.			
	Sub-group A. Normal Function. Weight for Age.	Sub-group B. Hyperfunction. Weight for Age.	Sub-group C. Hypofunction. Weight for Age.
	%	%	%
+ 1 stone or more	12	12	45
+ $\frac{1}{2}$ stone or more	18	12	60
- $\frac{1}{2}$ stone or more	33	56	10
- 1 stone or more	15	40	5
Within $\frac{1}{2}$ stone of normal standards	49	32	30

These figures are also of interest and seem to support the grouping on a clinical basis of these individuals. In Sub-group A, where clinically thyroid function is normal, 49 per cent. of cases are within  $\frac{1}{2}$  stone of the normal

standards. In Sub-group B, however, where hyperfunction is present, 40 per cent. of cases are below average weight to the extent of 1 stone or more, while 56 per cent. are below average weight to the extent of  $\frac{1}{2}$  stone or more.

The reverse condition is seen in Sub-group C, where hypofunction is present. Here it can be seen that 45 per cent. of cases are above average weight to the extent of 1 stone or more, while 60 per cent. are above average weight to the extent of  $\frac{1}{2}$  stone or more.

Thus it seems that a comparison of the physical measurements, especially weight, of these individuals with the average standards is of distinct value, for where the goitre is of the purely physiological type, little variation from the normal is found, but in others, where abnormal thyroid activity is present, a tendency is seen in hyperthyroidism for the individual to be below standard and in hypothyroidism to be above the average in weight for age.

*Menstruation.* A close relationship undoubtedly exists between the thyroid gland and the organs of reproduction, though its precise nature is not yet properly understood. Abnormalities of menstruation have been frequently described in thyroid disorders, and it is usually stated that both myxoedema and exophthalmic goitre may be accompanied by either menorrhagia or amenorrhoea.

Observations on the menstrual rhythm in adolescent goitre do not appear to have been made, so that the following details of our cases will show the prevailing tendency in the different groups. Table III gives the percentage number of cases in each group with the type of menstruation occurring.

TABLE III.

	Group I. <i>Colloid Goitres.</i>			Group II. <i>Exophthalmic Goitres.</i>
	Sub-group A. Normal Function.	Sub-group B. Hyperfunction.	Sub-group C. Hypofunction.	
	%	%	%	%
Menstruation not started	49	14	0	0
Menstruation normal	42	45	48	28
Menorrhagia	3	0	48	0
Delayed, irregular, and scanty menstruation	3	27	6	0
Periods of amenorrhoea	3	14	0	72

From this table it can be seen that the character of menstruation tends to vary inversely with the degree of thyroid activity, i. e. where hyperthyroidism is present the periods tend to be delayed, irregular, and scanty, or absent; while in the cases which show some evidence of hypothyroidism, there is more frequently a tendency to menorrhagia.

Another point of interest which is made evident by Table III is that, in all the groups of colloid goitres, menstruation is undisturbed in about half the cases, while in the exophthalmic group this is only true of one-quarter, but three-quarters of the latter have some degree of amenorrhoea.

The only other point on which emphasis might be laid is the large number of cases in Group I A in which menstruation has not started. This is not seen



# SOME FACTORS OF SIGNIFICANCE IN ADOLESCENT GOITRE 137

in the other groups, but it is really to be expected, for many of the cases of Group I are those of most recent origin.

TABLE IV. *Relation of Onset of Goitre to Onset of Menstruation.*

		Goitre appearing before Menstruation.	Menstruation appear- ing before Goitre.	Goitre appearing with Menstruation.
		%	%	%
Group I. Colloid Goitres.	Sub-group A Normal function	76	12	12
	Sub-group B Hyperfunction	42	31	28
	Sub-group C Hypofunction	33	41	26
Group II.	Exophthalmic Goitre	0	90	10

Table IV gives some interesting facts as to the relationship of the onset of goitre to the onset of menstruation. It is particularly to be noted that in three-quarters of the cases of colloid goitres (Group I A—function normal) the onset of the goitre precedes the onset of menstruation. On the other hand, in Group II (exophthalmic goitres) the onset of menstruation precedes the onset of goitre in 90 per cent. of cases. These figures seem to point to the conclusion that goitres developing before the onset of menstruation do not usually pass into the exophthalmic type, while those developing subsequently are frequently associated with abnormal thyroid activity.

## Basal Metabolism Estimation.

It is now generally conceded that basal metabolism estimations provide an accurate index of the state of functional activity of the thyroid gland. In hyperplastic and exophthalmic goitre the basal metabolism is raised above the normal level, in hypothyroidism and myxoedema it is depressed. A number of estimations of the basal metabolism have been made in the present series of cases. The method used is that of indirect calorimetry described by Cathcart: a sample of expired air is collected over a period of ten minutes in a Douglas bag, with the patient at rest and in the post-absorptive condition. This sample is analysed for its oxygen content, from which the patient's calorie production can be calculated and compared with the normal standards of Dubois. The results obtained are given in Table V, which shows the percentage number of cases in the different groups and their variation from the normal limits.

TABLE V. *Basal Metabolic Estimations.*

Percentage number of cases with B. M. R.'s.	Group I. Colloid Goitres.			Group II. Exophthalmic Goitres.
	Sub-group A. Normal function.	Sub-group B. Hyperfunction.	Sub-group C. Hypofunction.	
	%	%	%	%
Above +10 %	0	66	0	100
Within normal limits +10 % or -10 %	100	34	63	0
Below -10 %	0	0	37	0

These figures agree completely with the clinical grouping. In Group I, colloid goitres, in which thyroid function is normal, 100 per cent. of the cases have basal metabolic rates within the normal limits; when there is some hyperthyroidism (Sub-group B), only 34 per cent. of cases are within the normal limits, the remaining 66 per cent. having basal metabolic rates above +10 per cent.; of these 36 per cent. were above +20 per cent., while 64 per cent. were between +10 per cent. and +20 per cent. These figures are given to compare with Group II, exophthalmic goitre, where 100 per cent. of cases have basal metabolic rates above +10 per cent., but here 94 per cent. were over, and very considerably over, +20 per cent., and 6 per cent. only were below +20 per cent. This shows that the degree of thyroid toxæmia is much greater in the cases of Group II than in those of Group I B. Finally, in Sub-group C, where hypothyroidism is suspected, although 63 per cent. of cases fall within the normal limits, the remaining 37 per cent. have basal metabolic rates below -10 per cent. It is noteworthy also that in the hyperthyroid group there is no instance of a basal metabolic rate below the normal limits of -10 per cent., while in the hypothyroid group there is no instance of a basal metabolic rate above the normal limits of +10 per cent.

#### *Carbohydrate Tolerance Tests.*

The method of estimating the blood-sugar in these cases is that of Maclean (5). The fasting blood-sugar level was determined, 50 grm. of glucose were given, and further estimations of the blood-sugar were made at half-hourly intervals for two hours.

The majority of these cases were treated as out-patients, and a possible fallacy may exist, owing to the uncertainty of obtaining the true fasting level. For the sake of brevity the blood-sugar curves have been averaged and the result of each group has been shown as a composite curve. Chart I shows the composite curve obtained from the blood-sugar estimations made in ten cases of Group I, colloid goitres, Sub-group A, where thyroid function is normal.

Here it can be seen that, from a fasting level of 102 mg. of sugar for 100 c.c. of blood, there is a rise to a level of 168 mg. at the end of half an hour, and from this point the blood-sugar diminishes until, at the end of two hours, it has again reached normal. For purposes of comparison this curve has been accepted as normal, and the composite curves obtained in the other groups will be shown compared to it.

Chart II shows the composite curve obtained from seven cases of Group I B, i. e. colloid goitres with hyperthyroidism.

In this group the rise of blood-sugar was continued after the first half-hour and reached its maximum (163 mg.) at the end of one hour. The fall in the blood-sugar was considerably delayed and at the end of two hours it was still 152 mg.

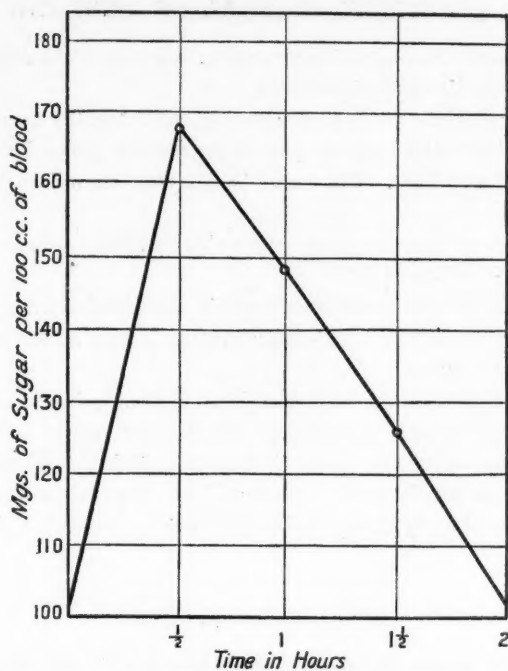


CHART I. Group I. Colloid Goitres. Sub-group A—normal function.

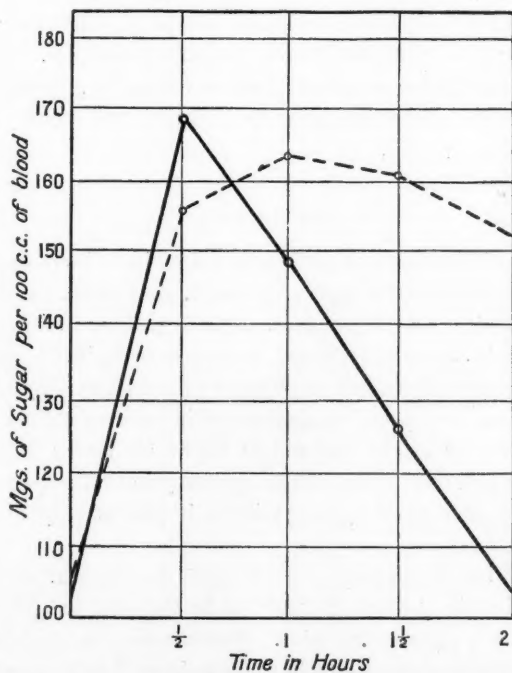


CHART II. Group I. Colloid Goitres. Sub-group B—hyperfunction.

Chart III shows the composite curve obtained from seven cases of Group I C, i. e. colloid goitres with hypothyroidism.

In this group all showed a higher fasting level than the normal, i. e. 112 mg. The maximum rise is the same as that in the normal group, but is not attained until the end of one hour. The curve is delayed, but not to the same extent as in Group II.

Chart IV shows the composite curve obtained from six cases of adolescent exophthalmic goitre (Group II).

This group shows the greatest changes in the blood-sugar curve. Not only is there delay, but a higher blood-sugar content is seen at the end of one hour than in the other groups.

From these tests it seems clear that in adolescent goitre, when clinical signs of abnormal function are present, the blood-sugar curves differ from those obtained in cases of goitre when there is no clinical evidence of abnormal function. In both conditions of hyper- and hypothyroidism there is a definite delay in the curve, but hyperthyroidism produces a generally higher blood-sugar content.

#### *Summary.*

It appears to us that a routine examination by the methods described is of very considerable value in estimating the significance of a goitre in adolescence. The examination should include careful observation of the clinical features, menstruation, the physical measurements compared with average standards, and estimations of the basal metabolism and sugar tolerance. In this way it is possible to form an opinion as to the extent to which the general health has been affected, and to obtain a rational basis for treatment and a guide to progress.

#### *Conclusions.*

1. A series of 100 cases of adolescent goitre have been examined. 79 per cent. correspond to the colloid type, 16 per cent. are cases of exophthalmic goitre, 3 per cent. adenomata, and 2 per cent. endemic goitres. In the colloid goitres thyroid function is apparently normal in 42 per cent., in 32 per cent. there is evidence of hyperthyroidism, and in 26 per cent. evidence of hypothyroidism.

2. Comparison of physical measurements in cases of colloid goitre with the average standards for height and weight shows (1) that a large majority are above height for age, but (2) that when hyperthyroidism is present the patients are below weight and when hypothyroidism is present they are above weight for age.

3. Menstruation is normal in about half the cases of colloid goitre, but if hyperthyroidism is present it tends to be delayed, irregular, and scanty; if hypothyroidism is present, excessive. Menstruation in exophthalmic goitre is normal in one-quarter of the cases; in the remainder it is frequently absent.

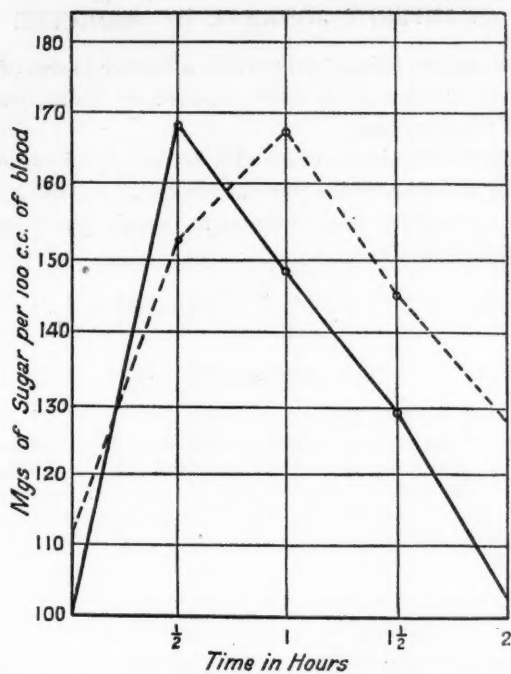


CHART III. Group I. Colloid Goitres. Sub-group C—hypofunction.

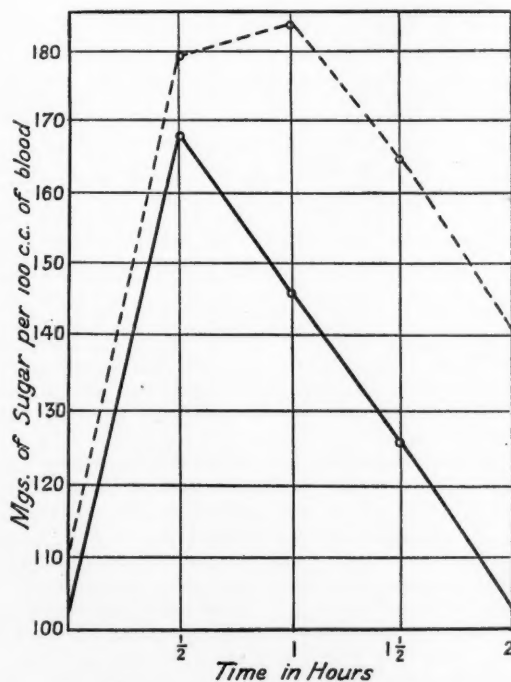


CHART IV. Group II. Exophthalmic Goitres.

4. Basal metabolism estimations provide a further means of grouping these cases; the results correspond to those obtained in adults, but the variation from the normal is not so great.

5. Blood-sugar curves in the cases with normal thyroid function differ from those obtained in the cases with abnormal function. In both hyper- and hypothyroidism there is a definite delay in the curve, though hyperthyroidism produces a higher blood-sugar content.

#### REFERENCES.

1. Marine, D., *Arch. Int. Med.*, Chicago, 1923, xxxii. 811.
2. Holt, L. Emmett, *Amer. Journ. Diseases of Children*, Chicago, 1918, xvi. 359.
3. Cathcart, E. P., *Journ. Roy. Army Med. Corps*, Lond., 1918, xxi. 339.
4. Aub, J. C., and Dubois, E. F., *Arch. Int. Med.*, Chicago, 1917, xix. 823.
5. Maclean, H., *Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes*, Lond., 1924, 60.



## A CASE OF VIRILISM ASSOCIATED WITH A SUPRARENAL TUMOUR: RECOVERY AFTER ITS REMOVAL<sup>1</sup>

By GORDON HOLMES

With Plate 5

THE case here recorded is that of a young woman in whom a large slowly growing tumour of the cortex of the right suprarenal body was associated with changes in the sexual organs (atrophy of the uterus, overgrowth of clitoris), disturbances of the sexual functions (cessation of menstruation for nine years), alteration in the secondary sexual characters (growth of hair, atrophy of mammae, change in the distribution of fat, and masculine appearance in limbs), and psychical changes (loss of erotic feelings, lack of modesty), all of which symptoms disappeared within a relatively short time after the removal of the tumour and left the patient again an apparently normal woman.

The long period during which the patient was under observation both before (two years) and after the operation (nine years) gives additional interest to the case. The histological and chemical examinations of the tumour were unfortunately not as complete as was desirable owing to the outbreak of the war immediately after its removal, but I have luckily been able to obtain the benefit of Professor Glynn's opinion on its structure and nature. It is also a matter for regret that the photographs of the patient's face and body during the time of her virilism have been lost owing to the disturbances of the war.

My patient, K. D., then aged 24 years, was first seen in July 1912. She came of healthy stock, her father being a Spaniard and her mother an Irish-woman. There had been fifteen children in the family, two of whom had died in infancy from measles and pulmonary complications; the others were alive and all in good health, with the exception of one younger sister who had previously been under my care for epilepsy. The seizures in her case were easily controlled by bromide and belladonna, and ceased nearly twelve years ago. In 1913 her father, then aged 65 years, developed a severe form of heart-block with epileptiform convulsions of the Stokes-Adam type, and he has since died of this condition. The Wassermann reaction in his blood-serum was negative.

The patient's health had been in every way excellent until the age of 17 years. Like all her sisters she had been a handsome well-built girl, with a rather fair complexion, delicate skin, and a profusion of brown hair on her head. According to her mother's statement she had, like all her sisters, a well-developed bust and large breasts from the age of 14 years. At about 18 years

<sup>1</sup> Received for publication July 30, 1924.

of age menstruation commenced, and continued regular and normal until her seventeenth year, when it ceased abruptly. From this time there were no menstrual phenomena, but every month or so she had slight attacks of vomiting, sometimes accompanied by headache, which she could not, however, identify with the menstrual periods. At about 19 years of age she noticed the appearance of fine hairs on her face, chiefly on the chin and upper lip, which slowly became longer and more profuse. Two years later a similar overgrowth of hair developed on her limbs and trunk, and about twelve months before she was first seen by me it extended to her cheeks and neck. Her general health remained undisturbed, but from the time her menses ceased she had gradually lost weight and had become, according to her mother, 'more and more flat-chested'.

There had also occurred a marked alteration in her mental as well as in her physical character. She had been, before any physical change was observed, fond of male society, and had been engaged in the ordinary flirtations of her age and class; in fact, from statements obtained later from her, it appeared that she was a very amorous, though perhaps not an exceptionally erotic young woman. She had, however, from the time of cessation of her menses lost all interest in the opposite sex and shown preference for the society of women. This may have been partly a result of the disfigurement due to the excessive growth of hair, but her manner while under observation suggested strongly that it could not be attributed to this only. She stated, however, that the sight of a pretty woman always made her wish to be like her.

The most striking feature when she was seen at the age of 24 in July 1912 was the presence of an excessive growth of hair on her chin, lips, and cheeks, of approximately the same distribution as in an adult male. The hair on the upper lip was straight, coarse, and brown, while that on the chin and in the area of the male beard was more reddish in colour and curly; here, however, the greater part of the excessive growth had been removed by electrolytic depilation. The hairs became more abundant on the lateral parts of the cheeks, especially in front of the ears where they joined the hairs of the scalp, but there was also an unnatural amount of fine downy hair on the rest of the cheeks. Her eyebrows were dark and normal, and there was no excess of hair on the forehead. That on the scalp was of an average amount and character.

The limbs, especially the lower, were also covered with short crisp dark hairs, such as are often seen in the male but never in the normal female; they were most profuse on the anterior and lateral aspects of the thighs and on the inner surfaces of the legs. The pubic hair extended up the abdomen and was continuous with similar coarse curly hairs of dark colour on the chest between and beneath her atrophied breasts. On the back there was a soft downy growth similar to that frequently seen in young adults, and in addition patches of short, crisp, black hairs in the scapular regions. The axillary hair was approximately normal in amount and distribution.

Even more striking perhaps than the excessive growth of hair was her general appearance and configuration, which strongly suggested masculinity, though there still remained evidences that she had been a handsome young woman. This was partly due to the sparseness and the distribution of the subcutaneous fat and to the muscular contours of the limbs. Her face was rather lean for a girl of her age, the lower jaw being unusually distinct and the malar bones rather prominent. Her hands were massive, her fingers thick and distinctly masculine, and the muscles of her arms stood out as they do in a thin but healthy young man. This masculine appearance was even more prominent in the lower limbs, especially in the buttocks and thighs, where the subcutaneous fat that gives the characteristic shape to the female hips was more or less absent. Their muscles, especially the quadriceps extensors and hamstrings, stood out when contracted as they do in an athletic male. The lack of subcutaneous tissue on the trunk also produced a striking resemblance to a boy of poor physique. The

power of the muscles, particularly in those of her limbs, was not so good as might be expected from their size.

Her breasts were very small, and, as far as could be judged from palpation, they contained little or no glandular tissue. The nipples and areolae were also pale and poorly developed. The clitoris, on the other hand, was very large and projected between the labia. The late Dr. Walter Tate, who examined her under an anaesthetic, found the uterus small, but discovered no other pelvic abnormalities. Her voice had not changed.

No signs of disease could be found in her visceral organs or in her nervous system, and no changes were detected in her skeleton by either inspection or radiographic examination. The sella turcica was not enlarged, and the thyroid gland seemed to be of normal size. Her glucose tolerance was slightly raised, being between 300 and 400 grm. Her urine contained no abnormal constituents.

Although she was undoubtedly sensitive of her condition and did not like her peculiarities being demonstrated, she exhibited less shyness and modesty when undressed and examined than might be expected from a girl of her social class. She admitted readily too that she had now none of that interest in men that she formerly had. She was intelligent and fairly well educated, and while under observation never exhibited any emotional or intellectual disturbances.

She was treated intermittently from July 1912 until June 1913 by thyroid extract in doses of 4 to 5 gr. a day, without, however, producing any noticeable change in her state. Extracts of the pituitary gland were also tried without effect. In September 1913 Dr. H. H. Dale, who had seen her with me, kindly prepared a special ovarian extract for intravenous injection and sent with it the following note on its mode of manufacture: 'The sheep's fresh ovaries were ground finely with twice their weight of 70 per cent. alcohol, the alcohol was evaporated off and the water residue filtered through a Berkefeld filter. It was not subjected to sterilization. Each c.c. of this extract represented 2 grm. of fresh ovarian substance.' She received intravenous injections, in doses of 1 c.c., at weekly intervals for about two months. She increased in weight during this time from 8 st. 4 lb. to 9 st. 1 lb., probably owing to her stay in hospital, but no other definite change was observed.

In February 1914 she complained of occasional pain in the right side of her abdomen, and examination revealed a swelling there, but it was not till June of that year that a tumour could be definitely made out. Then, on palpation of the abdomen, a rounded mass could be felt projecting below the right costal margin in front, which moved freely with respiration and when grasped could be moved laterally too. It displaced the right kidney, which could be felt separate from it, downwards, and the liver upwards. There were no enlarged glands and the patient's general health was excellent; the only change which had occurred in her condition since she had been discharged from hospital in November 1913 was a further increase of coarse hair on her face.

*Operation.* On July 7, 1914, Mr. Percy Sargent undertook the removal of the tumour through the loin. He found that it lay entirely outside the peritoneum and not attached to any of the abdominal organs, though closely adherent to the upper pole of the right kidney.

The patient bore the operation well and recovered rapidly from it. On August 13, thirty-six days after the removal of the tumour, she menstruated for the first time for nine years, and about the same time the hair on her face, and somewhat later that on the trunk, began to fall.

Owing to the outbreak of the European war it was not possible to examine her again till April 1920. Her menses had been since the operation 'as regular as clockwork', but rather profuse, lasting five to seven days. The abnormal hair had disappeared entirely from her face, limbs, and trunk, the only trace of its previous presence being the scarring due to the electrolytic depilation. She stated that it was chiefly at her menstrual periods that it had fallen, and that the

hair on her trunk had disappeared last. According to her own story the hair on her scalp had also fallen extensively about three months after the operation, so that she became 'nearly bald', but it had grown again and was now even more luxuriant and of a darker colour than it had formerly been.

Her 'figure' had also begun to develop again when her menses reappeared, and she now regarded herself in every respect normal. This was borne out by examination. There was now no excess of hair anywhere, her limbs had the ordinary plump female character, her bust was well developed, and her breasts were large and contained plenty of glandular tissue, though the nipples were small and the areolae around them pale and narrow. Even her clitoris, which had been remarkably large in 1913, had again shrunk to normal proportions. Her manner and conduct had altered too; whilst before the operation she never exhibited any reluctance to expose herself or to being examined, she now objected to undress fully, and could only with difficulty be persuaded to do so. She admitted, too, that she was now no longer indifferent to men, and during examination she exhibited unmistakeable signs of a highly erotic temperament.

She was again seen and examined in 1923 at the age of 35 years, nine years after the operation, and was still apparently normal in every respect.

The tumour when removed at the operation weighed 1,025 grm.; its maximum length was 17 cm., its greatest breadth 9.5 cm., while in thickness it measured 14 cm. It was enclosed in a tough greyish capsule which was broken only where the surgeon had torn it. No large vessels could be traced into the tumour, but a certain number ran in its capsule along its surface.

On section it presented an irregular variegated appearance, parts being of a reddish brown colour, becoming in places more greyish; other parts, in which some necrosis had apparently occurred, varied from yellowish to orange; and other areas were softer and very dark brown in colour, owing probably to earlier extravasations of blood into them. One pole consisted of smooth tissue resembling to the naked eye the medulla of the kidney; it contained a large firm-walled cyst filled with a blood-stained, spontaneously coagulating fluid. There was less undegenerated material towards the other pole, which contained a large cavity filled with pultaceous matter.

Portions of the tumour were placed in different fixing fluids and part of it was reserved for chemical examination, but unfortunately, owing to the outbreak of war, most of these specimens had disappeared when the opportunity to investigate them came again. The only material available now consists of a few sections prepared in 1914 from a piece of the tissue fixed in formalin, and a small portion that had lain in alcohol. Professor Ernest Glynn has kindly furnished me with a report on the histological appearances of these.

*Professor Glynn's Report.* 'I have carefully compared the section of the tumour from your case of suprarenal virilism with the descriptions of those from the other published cases, and with the actual sections from seven cases (for photographic reproductions from the sections of six cases, see Figs. 16, 17, 18, 19, 21, 25, *Journ. Obstet. and Gynaecol.*, 1921, vol. xxviii).

'The tumour resembles the zona reticularis of the suprarenal in the general character of the epithelial cells with their rather dense cytoplasm, due apparently to the presence of only a *small* quantity of lipoids (of course the presence or absence of lipoids cannot be *proved* in a paraffin section), and in the general arrangement and relative proportions of the epithelial cells, blood-vessels, and stroma.

'Nevertheless, the epithelial cells are not quite typical, for though some are polyhedral the majority are slightly elongated or spindle-shaped. Their longest diameter measures about 20 to 25  $\mu$ , and the nucleus 9  $\mu$ , compared with about 15  $\mu$  and 7  $\mu$  respectively in the zona reticularis of a normal adult suprarenal fixed in formalin.

'On the other hand there are none of the characteristic oblong, rectangular,



or large irregular cells, including giant cells, which are almost always present in these tumours; it is possible, however, that sections from other parts of your tumour might have revealed such cells. The blood spaces also are rather larger and more irregular than in the zona reticularis; those in the photograph are empty, for the erythrocytes have escaped, though they are present in certain parts of the section (Plate 5, Figs. 1 and 2).

*Comments.* The tumour is undoubtedly derived from the suprarenal cortex. Your description of its macroscopic appearance, particularly its variegation from the orange to yellow or brown areas, and the presence of blood extravasations and localized necroses, is similar to that found in most other cases.

'So far as I can judge from the examination of a single section the tumour is undoubtedly innocent; this is consistent with its encapsulation, and the fact that nine years after its removal there has been neither local recurrence nor local metastases; more than half these cases are malignant.

'The tumour appears to be the least atypical of any yet described, i.e. most like normal suprarenal cortex. This is consistent with the hypothesis that the epithelial cells were producing a large amount of internal secretion which presumably caused the extraordinary physiological changes present. The amount of the secretion would probably be less in proportion as the cells became atypical and malignant.'

Many similar cases have been already recorded. Glynn (7) has collected nine such cases of young women who, with the growth from the suprarenal cortex of tumours of similar structure to that in my case, developed hirsuties of the male type, almost invariably amenorrhoea, generally atrophy of the uterus and ovaries, atrophy of the breasts, and occasionally deepening of the voice.

There is further clinical evidence that disease of the suprarenal cortex, and especially such forms of disease as increase its functional elements, can influence the development or state of the sexual system. Thus congenital lesions, particularly bilateral cortical hyperplasia, have been often associated with pseudohermaphroditism, while unilateral cortical neoplasms occurring before puberty in girls have produced excessive growth of hair of the male distribution and hypertrophy of the external genital organs. In a few cases precocious growth, hirsuties, and precocious development of the sexual organs have been associated with these tumours in boys.

An interesting observation of analogous changes in a hen, associated with tumour of the suprarenal cortex, has been recently published by Berner (1). A white Leghorn hen, which was about one and a half years of age when killed, had during the preceding year displayed peculiarities which had raised considerable doubt as to its sex. It remained aloof from the other fowls of the farmyard, never laid eggs, and on palpation no eggs could be felt. It had spurs, a large upstanding comb, and a peculiar strutting gait, but it never crowed. A large lobulated tumour was found in the abdomen and metastases from it on the peritoneum, in the ovary and the lungs. The tumour arose from the cortex of the right suprarenal and resembled this closely in structure; its cells contained a large amount of lipid. There was also active proliferation of the cortex of the left suprarenal. The single ovary was hypoplastic and the oviducts abnormally developed, suggesting congenital malformation.

These observations go to justify the hypothesis suggested by Swale

Vincent (18), that a hormone (or hormones) secreted by the suprarenal cortex passes into the blood and exerts its action on the reproductive system. The case recorded here affords strong support to this hypothesis, for as the tumour tissue practically reproduced the normal structure of the suprarenal cortex, and as there was little divergence of the form of its cells from those of the mother tissue, we may assume that any secretion these might furnish would approximate in its properties to that of the original organ. In the second place, the disappearance of the virilism after the operation is evidence as strong as we can hope to obtain from clinical sources of the causal relation in which the tumour stood to it.

A somewhat similar case has been recorded by Knowsley Thornton (16). His patient was a married woman, 36 years of age, who had one child, aged 13 years. She had been subjected to oophorectomy six or seven years previously. After this operation she became 'covered all over with long silky black hair, and had to shave her face like a hairy man'.

Two years before she came under observation she had a sudden attack of pain in the left side of her abdomen, followed by uterine haemorrhage, the only recurrence of this since the removal of her ovaries. Her later symptoms were abdominal pain, indigestion, and constipation. In April 1889 a large tumour, which weighed approximately 20 lb., was removed together with the left kidney; its microscopical appearance 'reminded the observer of the structure of an adrenal'. Myrtle (14), under whose care she came soon after the removal of the tumour, states that 'the mammae had completely disappeared, and her cheeks, upper lip, and chin were covered with soft darkish down such as you see in a lad of 18 or 19, and her arms and forearms were also hairy'. He records her later history; she developed a large abscess subsequent to the removal of the tumour, which in July burst through the left lung. She consequently was seriously ill for several weeks and became very emaciated. In August she sailed for Canada. No further observations on her physical peculiarities are recorded, but in November 1889, seven and a half months after the operation, she wrote that she had improved very much in health and regained weight, adding, 'I am very much like my old self and have all the external appearances of other women'. This possibly means that the superfluous hair fell and that her breasts developed again. A note in the Royal College of Surgeons' Museum Catalogue, 3597 B., states that she died of intraperitoneal recurrence two years after the operation. The fact that the ovaries had been removed complicates this case; the amenorrhoea and atrophy of her breasts, and possibly part of the excessive growth of hair, may have been due to this.

Through the kindness of Sir Arthur Keith, Conservator of the Royal College of Surgeons' Museum, I was able to examine the tumour and obtain small pieces of it for microscopical examination.

It measures 10 by 7 inches in its chief diameters. Its surface is smooth and covered by a loose capsule. Its section in the recent state was described as showing large rounded masses of soft medullary tissue separated by bands of



fibrous tissue. Its colour has now disappeared, after thirty-five years in spirit, but a section of it suggests a variegated appearance similar to that of the tumour in my case. It was difficult to obtain satisfactorily stained sections, but some normal lipid could be demonstrated in the cells. Its structure resembled closely that of the normal suprarenal cortex, but large parts of it had undergone necrosis. Professor Glynn kindly investigated pieces of it for me and reported as follows: 'Two pieces of tissue were sent for examination: one from the surface, for it has a thick fibrous capsule; the other from the interior of the tumour. Paraffin sections were cut and treated with haematoxylin and eosin in the usual manner. They stained poorly, however, evidently because the tumour had been in preservative for about thirty-five years, and this made photographic reproduction unsatisfactory.'

'In spite of the deterioration there is no doubt that the tumour is derived from the suprarenal cortex (Plate 5, Figs. 3, 4). The appearance of the subcapsular portion, where preservation is best, almost exactly resembles that of your case K. D., both as regards the size, shape, and general arrangement of the epithelial tumour cells, and also of the connective tissue stroma and blood spaces.'

'There are only two real differences: first, the atypical epithelial cells are slightly more numerous and atypical, though no giant cells were found. Secondly, there is a very large amount of necrosis so characteristic of such tumours; the surviving or less necrotic epithelial cells in these areas often have a perivascular arrangement which I have seen in similar tumours, as those from the cases of French and Turnbull respectively.'

'The death of a patient from recurrence two years after the removal of the hypernephroma indicates its malignant nature, yet so far as can be ascertained from an examination of the two pieces of tissue the only signs of malignant tendency are the slight increase in the number of atypical cells and the marked necrosis, apart from the large size of the tumour.'

Collett (4) has recently recorded an interesting case in a female child who came of healthy stock; she was the youngest of a family of five normal children. Pregnancy and birth were natural, but at the age of 9 months the child had a bad attack of pertussis, and at 11 months bronchitis and convulsions.

Between 6 and 8 months a growth of hair was noticed by the parents in the region of the vulvae; this gradually became thicker and spread to the limbs and trunk when the child was about 13 months of age. At the same time she became heavy and fat, grew rapidly, and the voice became deep and rough.

When seen at the age of 18 months the child was considerably taller and heavier than the average; her head was large, her cheeks bulged, and her limbs were short and thick, but her hands and feet were well formed. Her voice was 'deep and rough, often rising to a squeak as in a boy at the time of the change of voice'. There was an abnormal growth of hair on the labia and mons veneris with a horizontal upper limit, and a dark growth on the thighs, shoulders, and back. Some hair had also appeared on the cheeks. The labia

majora and mons were well developed; the clitoris was a penis-like organ measuring 1.5 cm. in length, with a well-developed glans surrounded by a corona and covered by a prepuce which extended into the labia minora. There was a urethral groove on its under surface. The uterus was palpable per rectum. No prostate could be felt and the mammae were not developed. The pelvis was of masculine shape, and the degree of ossification of the bones at the wrist corresponded to that of a normal child of 3 years of age.

A tumour could be felt in the abdomen under the left costal margin. It was removed when the child was 2 years and 2 months of age. It was apparently surrounded by a fibrous capsule and presented a variegated appearance on cross-section. Some parts of it were necrotic, others resembled in structure the normal suprarenal gland, but some of the cells were more irregular in size and shape and contained several nuclei.

Two months after the operation there was a striking improvement in the appearance of the patient; the cheeks bulged less, the skin of the face had become smooth and childlike, and all the abnormal hair had disappeared, except for a few short dark hairs on the labia majora. The labia and mons projected less, the clitoris was perhaps smaller, and the trunk and limbs were less bulky, but the voice remained deep and hoarse. Even two years after the operation the clitoris was abnormally large and the voice was still masculine.

Suprarenal hypernephromata have also been removed by Hewetson (8) from an adult woman with typical virilism, by Hartmann (10) from a woman with no characteristic signs, and from children in the cases reported by French (6), Dobbertin (5), and Hijmans (11), but always with fatal results.

Bovin (2) has, however, recorded the case of a woman, aged 28 years, who had had two children, the youngest being then 10 years of age, in whom a tumour was successfully removed from the region of the left ovary; in Glynn's opinion it was most probably a suprarenal hypernephroma growing from an accessory suprarenal in the broad ligament. In her case the menses had ceased at the age of 19 years, and she grew a beard and excessive hair on her abdomen, but her breasts and external genital organs remained normal. Her uterus was described as the size of that of a virgin. Her menses reappeared two and a half months after the operation, and seventeen months after it the uterus was of normal size, but the hair persisted.

The cases already recorded, and especially those in which, after the removal of the tumours, the symptoms disappeared, afford evidence that must now be regarded as conclusive that an internal secretion derived from the cortex of the suprarenal bodies when in excess tends in women to diminish the female and increase the male primary and secondary sexual characters.

Krabbe (12) has recently criticized this conclusion, maintaining that we cannot argue from these observations that the cells of the suprarenal cortex possess such a function. The explanation he would offer is based on the views of Kohn and other embryologists, that the ovary is originally an hermaphroditic organ, its cortical part being female and medullary part testicular; the latter,

which remains rudimentary, is closely related in origin to the adrenal cortex, and he assumes that it is from cells of this nature included in the suprarenal that these tumours grow. It is, however, very improbable that all hypernephromata should take origin from such chance inclusions, and the majority of these tumours that occur in females before the menopause are accompanied by changes in the secondary sexual characters. Further, it is noteworthy that in many cases in which the tumour has approximated closely in structure to the normal suprarenal cortex, as in my case and that recorded by Bulloch and Sequeira (3), the abnormal symptoms were particularly well developed. The fact that analogous changes, or rather an increase of maleness, has been observed in boys with similar tumours is also a strong argument against this hypothesis.

The complete disappearance of the physical abnormalities on the removal of the tumour was a striking and perhaps unexpected feature of my case. Not merely did her beard and moustache and the unnatural profusion of hair on her limbs and trunk disappear, but her clitoris shrank, her breasts grew again, and her limbs lost their pronounced masculine appearance. In other words, the functional recovery that followed removal of the abnormal secreting tissue was accompanied by an equally striking structural restitution. We are, however, familiar with a similar improvement in the physical deformities that sometimes follow partial removal of the hypophysis in acromegaly, but a closer parallel may be found in such cases as those reported by Clement Lucas (13), Verebely (17), and Sacchi (15), in which the signs of precocious sexual development and the anatomical changes associated with it disappeared after the removal of the tumours of the ovaries and testes. Lucas and Verebely each removed ovarian tumours from girls of 7 and 6 years respectively, who had all the symptoms of precocious puberty, and obtained in each case a return to the normal state. Sacchi's case, a boy of 9½ years, was precociously developed both physically and mentally, had a considerable growth of hair on his pubis and in his axillae, and large well-developed genital organs. On removal of a tumour, which was diagnosed as an alveolar epithelioma, from one testicle, the hair fell from his pubis, his penis and the remaining testicle became small, and all signs of puberty disappeared.

There is, therefore, abundant evidence not merely that the active growth and development, in abnormal as well as in normal circumstances, of certain organs of the body, and especially the sexual organs and related systems, are dependent on internal secretions, but also that this growth when attained requires the continuous influence of these secretions and in their absence may regress.

Further, we may conclude that, in addition to the sexual glands proper (that is, the ovaries and testes), the hypophysis and perhaps epiphysis too, the cortex of the suprarenal bodies furnishes a hormone which plays an important part in the development and maintenance at a normal level of the genital organs and of the secondary sexual characters.

## REFERENCES.

1. Berner, O., *Norsk Mag. f. Lægev.*, Christiania, 1923, lxxxiv. 849.
2. Bovin, E., *Nord. Med. Arkiv.*, Stockholm (Partie Chir.), 1909, 3° F. ix. 1.
3. Bulloch and Sequeira, *Trans. Pathol. Soc.*, Lond., 1905, lvi. 189.
4. Collett, A., *Norsk Mag. f. Lægev.*, Christiania, 1923, xxxiv. 609. (Republished *Amer. Journ. Dis. Child.*, 1924, xxvii. 205.)
5. Dobbertin, *Beitr. z. Pathol. Anat.*, Jena, 1900, xxviii. 42.
6. French (see Glynn, *Quart. Journ. Med.*, Oxford, 1911-12, v. 157).
7. Glynn, E., *ibid.*, Oxford, 1911-12, v. 157.
8. Glynn, E., *Journ. Obstet. and Gynaecol.*, Lond., 1921, xxviii. 23.
9. Glynn, E., and Hewetson, J. T., *Journ. Path. and Bacteriol.*, Camb., 1913-14, xviii. 81.
10. Hartmann, *Travaux de Chirurgie*, Paris, 1905.
11. Hijmans, van der Berg, *Nederl. Tijdschr. v. Geneesk.*, Amsterd., 1915, 11, 2217.
12. Krabbe, K. B., *New York Med. Journ.*, 1921, cxiv. 4.
13. Lucas, R. Clement, *Clin. Soc. Trans.*, Lond., 1888, xxi. 224.
14. Myrtle, A. S., *ibid.*, Lond., 1890, xxiii. 154.
15. Sacchi, E., *Riv. sper. di Freniat.*, Reggio-Emilia, 1895, xxi. 149.
16. Thornton, J. K., *Clin. Soc. Trans.*, Lond., 1890, xxiii. 150.
17. Verebély, T., *Pest. Med.-Chir. Presse*, Budapest, 1912, xlviii. 306.
18. Vincent, Swale, *Surg. Gynaecol. and Obstet.*, Chicago, 1917, xxv. 194.

## DESCRIPTION OF PLATE.

PLATE 5, FIG. 1. Photograph of author's hypernephroma. The clear areas are empty blood spaces. Note the general similarity to the suprarenal cortex.  $\times 200$ .

FIG. 2. Camera lucida drawing of author's hypernephroma. The two clear areas are empty blood spaces. Cf. Knowsley Thornton's hypernephroma, Fig. 4; the slight differences are due to differences in the age and fixation of the two tumours.  $\times 500$ .

FIG. 3. Photograph of subcapsular portion of Knowsley Thornton's hypernephroma. It also shows the capsule and some empty blood spaces. Cf. Fig. 1.  $\times 200$ .

FIG. 4. Camera lucida drawing of Knowsley Thornton's hypernephroma. The clear areas are empty blood spaces. Cf. Fig. 2.  $\times 200$ .

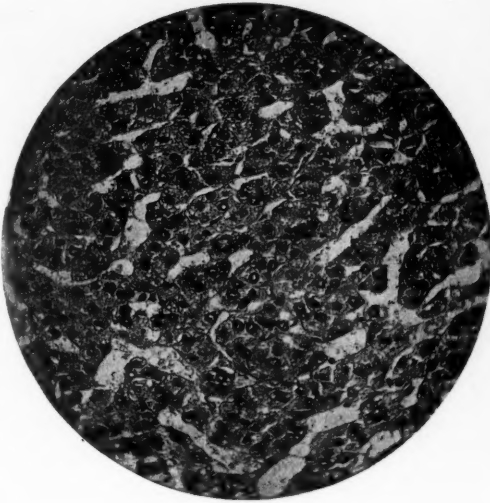


FIG. 1

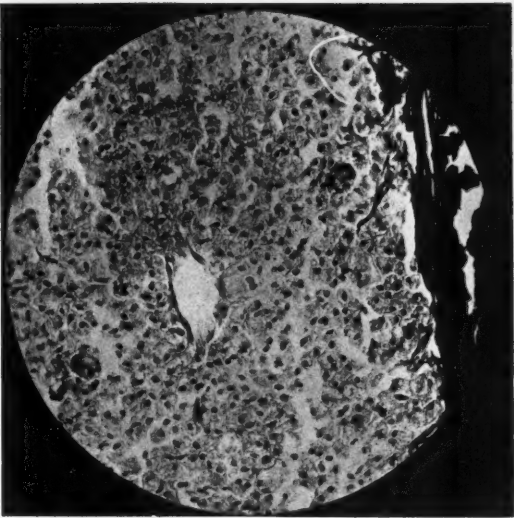


FIG. 3

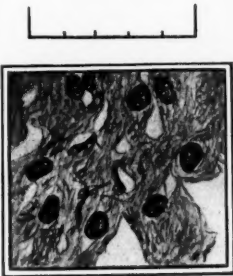


FIG. 2

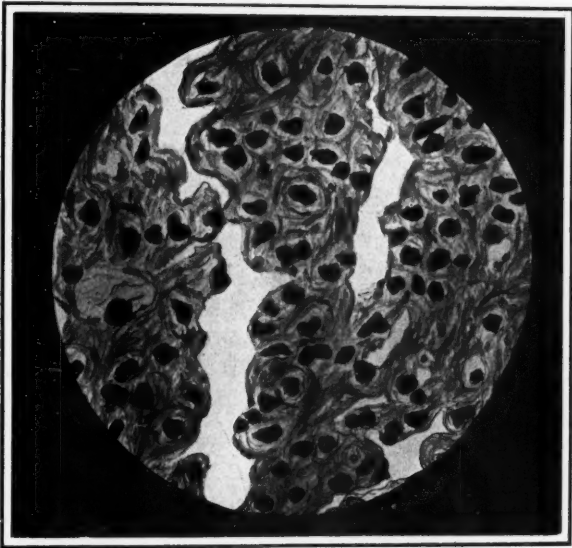


FIG. 4





## EPIDEMIC ENCEPHALITIS: THE SECOND WINNIPEG OUTBREAK<sup>1</sup>

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With Plates 6 and 7

It is now seven years since the disease known as epidemic, lethargic, or acute non-suppurative encephalitis first made its appearance. During these years the disease has come to occupy a position of supreme importance amongst the affections of the central nervous system, not only because of the danger of a fatal termination during the acute stage, but because of the insidious and disastrous sequelae which may follow in its wake. Often trivial in its initial manifestations, there is no disease more to be dreaded, for in many cases it may be said without exaggeration that it is the fortunate ones who die; the survivors long have a Damoclean sword suspended by a very slender thread above their heads.

An extensive literature has already collected round the subject, an excellent summary of which will be found in Prof. A. J. Hall's (1) recent Lumleian lectures. The experience of the north-west of Canada, however, and of the city of Winnipeg in particular, is worthy of special notice, partly because of the remarkable opportunity for study which the large number of cases has afforded us, partly because of the occurrence of two clearly defined outbreaks separated by an interval of three years, and partly because of certain peculiar features in the second epidemic which have not been dwelt upon in the literature.

The city of Winnipeg and the province of Manitoba have been visited by two epidemics, the first in the winter of 1919-20, the second in the winter of 1922-3. A few sporadic cases occurred in the interval.

During the first outbreak, which commenced at the end of 1919 and extended into the spring of 1920, there were 159 cases in Manitoba, 89 of which occurred in Winnipeg, a city with a population of less than 200,000. Of the 159 cases 112 were males, 47 females. There were 62 deaths, a mortality of 39 per cent. A complete post-mortem examination was made in 19 cases. Exactly a year had elapsed since the epidemic of influenza visited the city, so that even the most

<sup>1</sup> Received for publication May 23, 1924.

ardent advocate of the aetiological relationship between influenza and epidemic encephalitis could hardly find much support for his contention in this instance.

The second epidemic commenced in January 1923. In that month there were 32 cases in Manitoba, in February there were 75, in March 38. In all there were 165 cases, of which 108 occurred in Winnipeg, with a mortality of 25 per cent. The death-rate, therefore, was considerably lower than during the first outbreak. The majority of cases occurred among the poorer classes, and the Jews appeared to suffer much more than other sections of the community.

Although the disease is certainly infectious, it was only in very exceptional cases that the source of the infection could be demonstrated. A solitary case would occur in an isolated farm-house on the prairie, and the next case would turn up in an equally isolated spot thirty miles away. The infection must have been conveyed by healthy carriers or by persons presenting none of the classical features of the disease. Striking experimental evidence of this has been furnished by Levaditi (2), who demonstrated the virus in the mouth of a healthy man who had been in contact with cases of encephalitis, a virus with which he produced typical encephalitic lesions in rabbits.

In two of the 1919 cases a definite history of contact could be obtained, and in both there was a strong suggestion that the period of incubation was about fourteen days. (1) A man who lived on the prairie came into Winnipeg, and visited his brother's family for one day, returning home on the day following. Two weeks later both he and one of the girls in the house which he had visited developed encephalitis. (2) A rig-driver, who lived in a small town where there was no encephalitis, drove a doctor thirty miles into the country to see a case of the disease, and stayed for three hours in the house. Two weeks later he also developed encephalitis.

#### *The Clinical Picture in the Two Epidemics.*

A very interesting feature was the difference in the type of the disease in the two epidemics. Indeed, it was at times difficult to believe that one was dealing with the same disease. In the first epidemic the patient would lie like a log in bed with drooping lids or closed eyes, all the lines of expression ironed out, usually sunk in a state of stupor which no external stimuli could penetrate. A sharp question might arouse him, but all the flash and speed of the mind were gone; the dim rushlight of reason had almost flickered out. 'The great barons of the mind failed to rally to the standard, but sat each one at home, brooding on his own private thought.'

How different was the picture in the second epidemic. Body and mind were keyed to full activity. So restless was the patient that ordinary sedatives were of no avail. The muscles were in a state of constant activity. He would attempt to leap out of bed, or would spring from one end of it to the other. This was paralleled by a condition of mental excitement; words came in a torrent, rationally at first, but drifting away into an occupational delirium—the condition

to which the French have applied the expressive term of delirious drifts—all thought of sleep given up, a picture, it might be, of acute mania.

These, of course, are merely types. Cases of excitement and muscular activity were seen in 1920. Lethargy was a feature of many of the 1923 cases, although usually late in the disease. But the general impression on the observer of the two epidemics was quite different. The first was akinetic, the second hyperkinetic.

The seasonal incidence of the two epidemics was very similar. The first commenced at the beginning of November, the second at the beginning of January. Both reached their peak by the end of the second month, and then gradually tailed away. In January 1923 there were twenty-seven cases in Winnipeg, in February sixty-six, and in March fifteen.

*Hiccough.* The first epidemic was associated with an extensive epidemic of hiccough, which was not seen at all in the second. A number of doctors were among the sufferers. The attack lasted from one to five days, and during that time sleep in many cases was impossible. There must have been far more cases of hiccough than of encephalitis. It is true that hiccough seldom occurred in the patients with encephalitis, but, in spite of that, those of us who watched the cases of encephalitis and of hiccough became convinced that the hiccough was merely a myoclonic manifestation of infection with the virus of encephalitis. The fact that the two conditions were not more frequently associated may possibly be accounted for by the assumption that the attack of singultus immunized the patient against encephalitic manifestations of the disease.

*Rapid respiration.* One of the most curious of the many peculiar manifestations of the second epidemic was a great increase in the respiratory rate. This was sometimes a sequel, sometimes an accompaniment of the acute stage of the disease. Foster Kennedy (3) mentions one case in which the rapid breathing came on fifteen months after what was apparently a total recovery. Another of his cases had attacks of vomiting, which were apparently analogous to the rapid respiration and the hiccough seen in other patients.

Out of a number of striking examples of this condition the following history may be quoted. The case was a typical one of encephalitis with marked lethargy. During the acute stage the respirations were somewhat rapid, averaging 32 per minute. The temperature was slightly elevated. At the end of two weeks the temperature returned to normal, but the respirations increased in rate to 50 or 60 per minute. The rate gradually went up, and when the patient was discharged, very greatly improved, at the end of three months, the average rate was 70 to 80 per minute. Some four months later he was readmitted to hospital complaining of shortness of breath and weakness. On seeing the patient one was immediately struck by the very rapid and shallow respirations, which were between 80 and 90 per minute. During sleep the rate was only slightly slower. This rate was maintained until the patient was discharged a few weeks later.

*Peculiar sensory disturbances.* An even more curious manifestation of the second epidemic was the occurrence of certain sensory phenomena.

I was first made aware of this when I became a victim myself. On getting up one morning and brushing my hair I noticed that my scalp was curiously tender all over. During the course of the day the upper part of my face began to feel as if it had been badly sunburnt, for whenever I wrinkled my brow I was aware of the sensation familiar to every one during the first few days of a holiday in the open. Next day the condition was worse, and I hardly dared to touch my head or face in the distribution of the first division of the fifth nerve. The hyperaesthesia gradually passed away, and was gone in the course of four days. At no time was there any actual pain, nor did I experience any malaise nor disturbance of my general health.

I thought nothing about the matter until I discovered to my astonishment that many of my medical and other friends were having somewhat of the same experience. One of my technicians had extreme tenderness of the scalp associated with marked malaise. My laboratory boy complained of feeling seedy, and remarked that he could hardly pull on his shirt because the skin of his back felt 'as if it had been sunburnt'. One doctor felt out of sorts on Tuesday and vomited several times. On Wednesday he felt so weak that he stayed in bed. On Thursday he had pain in his left ear when swallowing, which lasted for twenty-four hours. On Friday he was aware of marked hyperaesthesia of the scalp and the left side of the face, so that he could hardly bear to wear a hat. The hyperaesthesia of the face was curiously limited to one side, for the pressure of the eye-glasses caused great discomfort on the left side of the nose, but none on the right. For five or six days he felt weak and seedy, but at the end of that time he regained his usual health.

One of my students had the following experience: One day he noticed that when he brushed his hair there was marked tenderness on the top and back of the head. The sensitiveness then passed down to the temporal region on each side, and finally the gums were affected. This gradual descent occupied about seven days. By the end of that time the top of the head had recovered, but the temporal regions were still quite tender. Shortly after the involvement of the gums he noticed an area of tenderness on the outer side of the middle of the left leg. This lasted for four or five days, and about a week later the gums cleared up. The duration of the whole condition was about three weeks. At no time was there any constitutional disturbance.

A neurologist developed marked hyperaesthesia of the scalp and face in the distribution of the first and second divisions of the fifth nerve. After a few days this cleared up. A week later he developed hyperaesthesia along the ulnar side of the left arm and on the right side of the thorax. One of the house-surgeons had a very similar experience, the hyperaesthesia of the arm and body coming on some time after that of the face.

A lady, 42 years of age, one day noticed a sensation of warmth at the root of the neck, particularly in the suprascapular region. Next day this had developed into a definite feeling of heat, and it had extended upward so as to involve the entire scalp. On the following day she complained of burning and great tender-

ness all over the scalp. Two days later the symptoms subsided and rapidly disappeared. At no time were there any symptoms of constitutional disturbance.

One would not have thought anything of any one of these cases occurring alone, and would probably have attributed the symptoms to some form of neuritis, but the fact that there was a real epidemic of the condition, and that this epidemic synchronized with an epidemic of encephalitis in which the most extraordinary symptoms were encountered, aroused our suspicions.

On carefully inquiring of the encephalitis patients it was soon discovered that a number of them had had a similar experience at the commencement or during the course of their illness, the hyperaesthesia of the face being sometimes associated with neuritic pains in the arms, sometimes not. Tenderness of the scalp when brushing the hair was present in seven out of fifty cases cross-examined on this point, but in no case was it recorded in the history, for it had never occurred to the patient to mention it.

Moreover, there were occasional cases which served to bridge the gap between those persons who remained quite well and typical cases of encephalitis with hyperaesthesia. One doctor developed a temperature of 101° F. and felt out of sorts. Next day he was all right, and his temperature was normal. On the third day he noticed hyperaesthesia of the back of the hands and wrists. This lasted for several days. A week later the temperature rose to 101° F. and remained up for a few days. At the same time he began to suffer from pains in the left arm, which passed up to the shoulder and were diagnosed as neuralgic. Then intractable insomnia developed, and spasmodic twitchings of the left arm appeared. The case was diagnosed as an atypical one of encephalitis.

Hyperaesthesia of the head, of the arms, and of the body have therefore been observed (1) in typical cases of encephalitis, (2) in atypical cases, (3) in non-encephalitic persons who were definitely ill, and (4) in those who appeared to be perfectly well. One is forced to the conclusion that the peculiar disturbances of sensation which were so common amongst one's acquaintances in the city during the epidemic of encephalitis were examples of 'formes frustes', and that the infection was very much more widespread than was generally supposed. The idea that it was all a matter of suggestion cannot be entertained, for none of the victims knew that there were fellow sufferers.

*Mode of onset.* During the first epidemic the disease usually began with malaise, diplopia, and lethargy. In its mode of onset it was very variable. Sometimes it was so sudden as to be most misleading. One patient was so suddenly overcome with weakness that he would have fallen to the ground but for assistance. A child of 18 months became so ill when down town with its mother that it had to be taken at once to the hospital. A provisional diagnosis of intussusception was made, but the subsequent autopsy showed typical and severe lesions of encephalitis. In a few cases the onset was so acute as to suggest a cerebral haemorrhage.

In other cases the onset was so gradual and insidious that a correct diagnosis was not made for a considerable time. One woman complained of malaise and



severe headache for three weeks, and it was not until the end of a month that the appearance of fresh symptoms enabled a definite diagnosis of encephalitis to be made.

In the second epidemic the mode of onset was quite different. The cases belong to two main types which may be classed as sensory and motor. In sixty-three cases which I was able to study personally, 54 per cent. belonged to the sensory type, 40 per cent. to the motor. These figures include some cases in which the initial symptoms were both sensory and motor, so that there were a number of cases which presented neither well-marked motor nor sensory symptoms at the outset.

*Sensory onset.* The sensory symptoms were mainly neuralgic in type, and at first many cases were diagnosed as neuritis. The pain would start in one part of a limb, travel along it, and often pass to the opposite side. Not infrequently it commenced in the thumb or the thenar eminence, passed up the arm, and left that limb only to reappear on the opposite side. In one case the pain persisted in the thumb for several weeks.

The pain usually began in the arms, and we noticed that with curious regularity the left arm was affected in preference to the right. The left side of the face was also that most commonly involved. Perhaps the part most frequently affected was the ulnar side of the forearm. The pain may commence, however, in any part of the body, and may prove most perplexing to the physician. Take, for instance, the following case: A school teacher, 26 years of age, was seized with severe pain in the right groin and hip, which was thought to be due to appendicitis. So severe was the pain that large doses of morphia were necessary. The pain passed down over the iliac crest on to the thigh, following the distribution of the ileo-inguinal nerve. It was accompanied by hyperaesthesia so intense that the weight of the bed-clothes proved intolerable. On the other hand, there was no pain on deep pressure. The temperature and pulse were normal. The patient escaped a laparotomy, but remained a complete mystery till four days later, when the muscles of the affected part of the right leg began to twitch. The muscular contractions became general, she developed a marked occupational delirium, was teaching all the time, sank into a state of lethargy and finally coma, and died on the twelfth day. Two days before death the temperature shot up to 104° F.; this was the first rise since the onset of the illness. Such a case in the early stages would puzzle the very elect. In another remarkable case the first pain felt was in the perinaeum, and the patient was admitted to a surgical ward with a diagnosis of prostatic abscess. This case also proved fatal.

It is evident, therefore, that sensory disturbances formed a most important part of the clinical picture. The disturbance took the form of hyperaesthesia or of actual pain. It occurred at the onset or during the course of the disease. In our cases the onset was sensory in character in 54 per cent. of the cases, and in 58 per cent. there were pains at some stage of the illness.

Sensory disturbances were not a striking feature of the first epidemic, but



they were observed in a number of instances. They usually took the form of neuralgic pains, which were most marked in the shoulder and upper part of the arm, but occasionally involved the hands and even the legs. In one perplexing case the pain commenced in the right hand, and extended up as far as the shoulder. It then spread to the left arm, the right leg, and finally the left leg. All four limbs were affected at the same time, and a diagnosis of peripheral neuritis was made. Three weeks later, fever, ptosis, and other characteristic signs of encephalitis appeared, and the patient slept for nearly a month.

The explanation of these pains is still a matter of debate. Are they central in origin, depending on lesions in the thalamus, or are they due to irritation of the posterior nerve-roots? The following case, which occurred during the first epidemic, seems to lend support to the latter view: A woman, 45 years of age, developed severe neuralgic pains on the left side. A couple of days later the characteristic lesions of herpes zoster appeared in the area of distribution of the pain. The herpes cleared up, but the pain continued, and eight days later ptosis, tinnitus, drowsiness, and a characteristic facies showed that the disease was epidemic encephalitis.

*Motor onset.* Frequent as was the sensory mode of onset, it was only to be expected that abnormal movements would be the initial symptoms in many cases in an epidemic whose salient characteristic was hyperkinesis.

In 40 per cent. of the cases studied abnormal muscular contractions were noticed at the very beginning of the illness. This is in marked contrast to the experience in the first epidemic. In the early stages of that epidemic myoclonic movements were very seldom seen, but towards the end there were a number of cases in which muscular spasms formed a striking feature in the clinical picture.

The movements in the first epidemic were of various descriptions. Some were fibrillary, recalling those of progressive muscular atrophy. Others were more rhythmic in character, affecting especially the hands, and resembling the familiar cigarette-rolling movements of paralysis agitans. Others again were much coarser, like the movements of chorea or athetosis. In four cases there were clonic spasms of the rectus abdominis. One characteristic case of encephalitis with clonic rectus spasms manifested rapid spasmodic movements of both legs, 84 per minute in the right leg, 48 in the left. I mention this last case because of the light which it throws on another obscure case about to be described. Apart from these abnormal movements during the acute stage of the disease there have, of course, been many examples of the characteristic Parkinsonian rhythmical movements which come on so late as to warrant their inclusion in the group of sequelae.

In the second epidemic the motor disturbances occupied a commanding position. Indeed, if we seek to describe the two epidemics in general terms we may call the first akinetic, the second hyperkinetic. Not only was the onset motor in 40 per cent. of the cases studied, but in 82 per cent. of the cases there was hyperkinesis at some stage of the disease.

Hyperkinesis, of course, is a rather general term. To be more precise the

following examples of muscular excitability were observed: (1) myokymia—a fine quivering of the muscles; (2) rhythmic tremors—the familiar Parkinsonian movements; (3) myoclonia—spasmodic muscular contractions, such as those of the rectus abdominis already referred to; (4) choreiform movements; (5) athetoid movements; (6) convulsions.

1. Myokymia was very frequently seen both in the muscles of the trunk and of the limbs.

2. Parkinsonian tremors were not characteristic of the acute stage. I did not observe any example of it in the hands. It was observed in one place, however, and that an interesting one. A number of patients showed a peculiar rhythmical movement of the lips, an opening and shutting of the mouth, which reminded one so much of a fish breathing that I came to refer to these as the fish movements. They were only observed in patients in a lethargic or stuporose condition, and their significance will be referred to later.

3. Myoclonia in one form or another was of frequent occurrence. Any of the muscles, either of the trunk or the limbs, might show regular or irregular spasmodic contractions. It was therefore a very characteristic symptom. The question came to be, was it possible to diagnose a case as one of epidemic encephalitis from the occurrence of myoclonia alone? A boy, 15 years of age, was admitted to hospital suffering from a peculiar myoclonic jerking of the left leg, which commenced two days previously. The leg was jerked violently about fifty times a minute. By an effort of the will the movements could be controlled for a few minutes. The boy felt perfectly well in every other way; there was no temperature, no diplopia, no pain, no hyperaesthesia. He lay there, apparently in perfect health, with his leg jerking away as if he had hiccough in the part. To label such a case encephalitis appears at first to be rather absurd, and yet the characteristic case of encephalitis already described had contractions of the leg which were essentially similar.

Very many of the myoclonic cases started with neuralgia in the affected part. A typical case would develop neuralgia on one side of the face for a week; then it would pass to the other side. The first side would then manifest myoclonia, which would again pass to the other side. The arms and then the legs might be successively involved. The myoclonic cases were those with the worst prognosis, and many ran the gamut of intractable insomnia, delirium, stupor, coma, and death.

4. Choreiform movements were very common, often amounting to little more than a slight twitching or shrugging of the body. In other cases the movements were of the most violent character. A girl, 22 years of age, developed malaise, diplopia, and fever, but when admitted to hospital she presented so characteristic a picture of violent chorea that for many days it was impossible to arrive at a definite diagnosis. So violent were the movements of the arms and legs that the skin of these parts became severely chafed. She was unable to lie still for more than a minute or two, and sleep was out of the question. She could, however, completely control the spasms for a few

moments, and could lift a glass of water from the table and drink it without spilling any.

5. True athetoid movements were rarely seen, but twisting and contortions were common.

6. Convulsions were very uncommon. There were two cases in the second epidemic. A young Jewess, in good health, felt the left arm beginning to ache. The pain radiated up to the shoulder and neck. She was unable to sleep because of the pain. Next day there was headache, nausea, and vomiting. The affected arm began to shake, there was twitching of the face, diplopia and slight facial paralysis developed. The picture was a typical one of epidemic encephalitis. When her physician was examining her she suddenly went into a violent convulsion. After the convulsion there was a double Babinski sign. During the next few days she had a series of convulsions, but eventually made a good recovery.

In addition to these various forms of hyperkinesis there was frequently a condition of general muscular excitability which made it impossible for the patient to remain at rest for more than a few moments. This varied in degree from a mere tossing about in bed to a condition in which the patient had to be forcibly restrained and held down in bed both by night and day.

*Muscular rigidity.* The muscular rigidity of epidemic encephalitis, dependent probably on lesions of the corpus striatum, is so well recognized that it need not be described in detail. We had a number of interesting examples of the difficulty which a patient experiences both in initiating and terminating a muscular movement. The long-drawn-out contraction is particularly striking. When a patient stops whistling, the pouting of the lips may continue for a long time after the effort has ceased. The tongue when protruded is withdrawn very slowly. The slowly fading smile is another example of the same thing. Instances of catatonia, of the Parkinsonian mask, and of the characteristically stiff walk were common.

*Cranial nerve disturbance.* Symptoms pointing to disturbance of the cranial nerves, particularly those whose nuclei are grouped around the aqueduct of Sylvius, were present in 82 per cent. of cases in the second epidemic. In spite of this high incidence, involvement of the cranial nerves was not such a characteristic feature of the second epidemic as of the first, in which it was present in nearly every case. A marked characteristic of the 1919 cases was the transient and fleeting nature of the disturbances. Not only were they present one day and gone the next, but they sometimes varied from hour to hour. A patient would have marked diplopia when first examined, but six hours later his vision would be normal, and the same was true of some of the cases of facial palsy. Manifestations so fleeting and evanescent could hardly be due to lesions in the nuclei of the cranial nerves. In several of our cases we found that the nerve-fibres during part of their intracerebral course were being pressed upon by greatly dilated vessels, some of which were surrounded by the typical perivascular collar. On removal of the vascular pressure the symptoms of cranial nerve palsy would rapidly disappear.

Optic neuritis was only observed in rare instances, and was never at all marked. In the first epidemic, however, there were two instances of marked optic atrophy coming on a few months after the original illness. In one of these there was marked retinal degeneration, the result, apparently, of a low-grade inflammation.

*Mental condition.* Reference has already been made to the different mental picture in the two epidemics. The 1919 case was lethargic and apathetic, he appeared to be cut off from the outside world, perhaps by lesions of the thalamus which interrupted the flow of incoming sensations. The 1923 case presented an entirely different picture. He was very much awake and would talk incessantly, rationally at first, but soon drifting off into incoherence. His occupation formed the main subject of his conversation: the teacher was continually teaching, the merchant was casting up accounts, the builder planning new houses—a true occupational delirium.

Even at the beginning of the earlier epidemic, however, there were cases which were marked by excitement rather than by lethargy. For instance, a man on getting up one morning began to pray. As this was far from usual with him, his wife feared that he must be ill. He continued at his prayers all the morning, and then became excited and violent. As he persisted in crawling under the bed he had to be strapped down to the mattress. For several days he remained in an acutely maniacal condition, became gradually weaker, and died on his way to hospital. At no time was there a suspicion of encephalitis lethargica, but autopsy revealed the characteristic lesions in the medulla, pons, and mid-brain.

Although the majority of the 1923 cases were far from lethargic in the early stages, 56 per cent. of them developed lethargy sooner or later, and many of the cases were still distinctly drowsy when discharged from hospital. A change in mood was noticeable in most of the patients. At first they were euphoric and mildly exalted, but they usually finished up in a state of depression. This depression was of a passive character, an *ahedonia* or loss of pleasure, a mild melancholy, with none of the mental anxiety of the true melancholic.

One or two patients developed what might be considered as a Korsakoff's syndrome, with amnesia, disorientation, and a remarkable tendency to confabulation.

A few of the children displayed the mental deterioration and normal perversion so graphically described by Grace Anderson (5). The best description one could give of one of these boys was that he was a perfect little devil, to such an extent did he seem to exhaust his ingenuity in devising modes of wickedness.

Hallucinations of sight were a marked feature of the later epidemic, but not of the earlier. They were present in 26 per cent. of the cases. The hallucinations were of a curiously objective and palpable character. I have seen a patient stretch out his hand for a glass of water which existed only in his imagination, and patients would frequently say that one of their relatives had been sitting

beside them. The hallucinations never appeared to be of a terrifying nature.

*Inversion of the sleep rhythm.* In the first epidemic, particularly in the later stages, insomnia was a minor feature in a number of cases. It was not, however, until the second epidemic that we encountered the marked inversion of the sleep rhythm, the nocturnal insomnia, which was such a striking feature of many of the cases. Some degree of insomnia was present in 76 per cent. of the 1923 cases. The insomnia proved quite resistant to ordinary hypnotics. Indeed several patients became wildly excited after ordinary doses of such sedatives as morphine and hyosine.

As a rule the nocturnal insomnia was associated with diurnal somnolence. The worst examples were seen in children. After a day spent in slumber the unhappy child would awaken about four o'clock in the afternoon, and become more and more awake, restless, and talkative, with an ever-increasing excitement which reached its climax round about midnight. As the dawn broke, exhaustion appeared to supervene on excitement, lethargy crept on, and by the time the child should have been going to school he would be deep in sleep. One of the cases, a boy 6 years of age, has developed considerable enlargement of the thyroid gland since the commencement of the attack.

*Cerebro-spinal fluid.* Little information of a direct character was obtained from examination of the cerebro-spinal fluid. The findings in the two epidemics were very similar. A fluid normal as regards cells and protein was the rule rather than the exception, and served to distinguish the cases of encephalitis from the two conditions with which it may readily be mistaken, namely, tuberculous meningitis and acute anterior poliomyelitis. The pressure was almost invariably increased, and a slight protein increase and lymphocytosis were fairly frequent. The sugar content in the cerebro-spinal fluid was increased in all the cases in which it was examined for, the highest reading being 0.094 per cent. In none of these cases was there an increase in the blood-sugar.

#### *Duration of the Disease.*

One of the most important phases of the encephalitis problem is the duration of the disease. At first sight it appears obvious that the disease is one characterized by an acute attack, a slow convalescence, and the frequent development of disastrous sequelae, the result of the original cerebral lesion. It may be that some, perhaps many, cases run this simple course. It is equally certain, however, that in others the course is very different.

One of our cases remained ill for five months. During the whole of that time it was evident that he was suffering from an active cerebral infection. Every few days the temperature would go up to 103° F., and would then return to normal. In the third month of his illness myoclonic contractions began to appear, affecting first one part and then another. He became extremely emaciated and developed a ravenous appetite. (Many of the cases displayed an abnormal



appetite, and the nurses were in the habit of saying that a patient must have encephalitis because of the size of his appetite.) The cerebro-spinal pressure was greatly increased; as much as 80 c.c. of fluid would be withdrawn at one time. At the end of seven months the patient died. Most unfortunately it was impossible to obtain permission for an autopsy.

In such a case it is impossible to avoid the conclusion that the virus of the disease continued to live for months in the brain, producing a succession of fresh lesions. The well-known case described by Economo illustrates the same idea. His patient was taken ill in April 1917 and died on January 7, 1919. Apparent recovery was followed by several severe attacks separated by periods of remission. The post-mortem findings were profoundly significant, for not only were extensive old lesions found, but many acute lesions as well. In a case described by Schaller and Oliver (6), the patient had an acute attack of encephalitis, showed marked improvement for a year, then had a relapse, and died fourteen months after the original illness. The autopsy showed many recent lesions, including haemorrhages, in addition to old lesions. The experimental evidence is in line with these histological observations, for Levaditi and Harvier succeeded in transmitting the disease to rabbits from the brain of a patient who had been ill for six months.

We are confronted, then, with the possibility that the virus of encephalitis may linger in the brain like the virus of syphilis. There may be only primary and secondary lesions, or there may be tertiary lesions coming on months or years afterwards. If this be the case, many of the symptoms which are usually looked upon as sequelae due to fibrosis should rather be regarded as tertiary manifestations of a still active disease.

It is possible that there may be another point of resemblance between epidemic encephalitis and syphilis. After the primary inoculation the syphilitic virus becomes widely disseminated throughout the body before settling down in the tissues in which the most serious lesions are to be produced. The same may be true for encephalitis, for, in addition to degenerative lesions in parenchymatous organs, in three of our cases there were numerous petechial haemorrhages under the pericardium and the pleura, and on the under surface of the diaphragm, findings strongly suggestive of a general infection. In none of these cases had there been any convulsions.

If this view of the disease be correct we might begin to speak of late manifestations rather than sequelae of the disease. For the term sequel implies that the disease has run its course, and that any further symptoms which may appear are the result of the irreparable damage to the brain, and not of fresh activity on the part of the virus. Hall, in the paper already referred to, suggests that arterial degeneration may be the cause of the development of late symptoms, but the facts cited above would appear to make it much more probable that the real explanation is to be sought for in a period of latency followed by a recrudescence of activity on the part of the encephalitic virus.

Bassoe (7), in a recent discussion, mentions several instances of late



Parkinsonian symptoms developing in young persons as long as three years after the initial illness, the patients having remained perfectly well in the interval. He is inclined to attribute these late manifestations to a long dormant infection rather than to a slow fibrosis resulting from the initial damage to the brain.

A case described recently by Leiner (8) supports this view of what are usually termed sequelae. The patient was a boy, 8 years of age, who had an attack of encephalitis in September 1919. A month later he developed reversal of sleep, change in character, and other disturbances. A year afterwards he began to suffer from paroxysmal attacks of rapid respiration. His character had completely altered. 'He kept the staff, nurses, and children under constant tension. No one knew what he would do next. He vaulted into the beds of the other children, tweaked their noses, pulled their ears, and took possession of and destroyed their toys or crackers.' Soon after this he passed through an attack of lobar pneumonia with marked cerebral symptoms. When he recovered he proved to be a new boy, for not only did his strange paroxysmal respiratory attacks never return, but his character was completely restored to its former normal condition. For more than a year he has remained perfectly well. Such a result is in line with the well-known effect of an acute upon a chronic infection (the basis of the treatment of general paresis with malarial parasites), but by no stretch of the imagination could a gliosis or an arterial degeneration be benefited by an attack of pneumonia.

#### *Pathology.*

The pathological lesions found in the central nervous system in epidemic encephalitis have been so fully described by Buzzard and Greenfield (9), Marinesco (10), and many other writers, that nothing is to be gained by giving a detailed account of the ordinary lesions which we encountered and which are already so well known. The gross and microscopic changes observed in the brain in both epidemics were those which are familiar to all. A brief summary, however, of the principal lesions found in the first epidemic, and already described in detail by the present writer in a previous paper (11), may be of interest for comparison with the changes in the second epidemic.

*First epidemic.* Autopsies were performed in sixteen cases. The principal change was an interstitial inflammation accompanied by more or less parenchymatous degeneration, the latter, however, bearing no direct relation, neither in locality nor intensity, to the former.

The most evident lesion, and the one which when present at once served to clinch the diagnosis, was the well-known perivascular collection of wandering inflammatory cells, of which the principal were the lymphocyte and the plasma cell. Elongated cells, probably derived from the vascular endothelium, were occasionally seen. In only one case were polymorphonuclears present. A diffuse infiltration of the brain, particularly in the periaqueductal region, was frequently

found. Common as were these cellular lesions, it will soon be seen that it was a mistake to rely upon them too implicitly, for in some of the most acute cases they apparently did not have time to develop.

Great vascular dilatation, accompanied in many cases by thrombosis and haemorrhage, was the most constant finding. This congestion was present in every case. It was most frequently found in the lower part of the pons, immediately under the floor of the fourth ventricle. The haemorrhages which were so frequently present did not bear any constant relation to the dilated vessels. In places they were grouped around a greatly distended vessel; in others the source of the haemorrhage could not be detected.

The cases in which haemorrhage formed the most striking feature are worthy of special mention. In the first the patient, a man 40 years of age, after a week of malaise and headache, suddenly became paralysed, and was plunged into a profound and sudden stupor. On admission to hospital he was completely unconscious, the left arm and leg were paralysed, there were twitchings of the right arm and leg, all four limbs were spastic, the blood-pressure was 80, and the temperature 98° F. The patient lay on his back, breathing stertorously, the picture of cerebral haemorrhage. He died next day, the temperature rising meanwhile to 103° F.

At autopsy the left cerebral hemisphere felt unduly soft, and showed distinct bulging in the parietal region. On section there was intense congestion of the entire brain, and the left hemisphere was so thickly studded with minute haemorrhages as to have a distinctly pink colour. Microscopically the innumerable haemorrhages scattered throughout the cerebrum were seen to be curiously spherical in outline. In the centre of most of the haemorrhagic areas was a small vessel, with greatly swollen endothelium, and surrounded by a few cells, almost all of which were polymorphonuclears. No perivascular collars of inflammatory cells could be found either in the cerebrum or the mesencephalon, and the diagnosis of encephalitis was in grave doubt until typical collars were found in the lower part of the pons, where, however, there was no haemorrhage. This case showed us that a diagnosis of encephalitis could be made in the complete absence of perivascular infiltration, an opinion which was confirmed by our subsequent experience.

The second patient was a girl of 7 years, who died after two days of illness, characterized by headache, vomiting, dimness of vision, ringing in the ears, and convulsive movements of the right arm and leg, and finally the left leg. Microscopic examination showed numerous petechial haemorrhages throughout the mid-brain, pons, and medulla, with thrombosis of many of the vessels. None of the vessels showed any perivascular infiltration, the acuteness and short duration of the illness no doubt accounting for the absence of this protective reaction.

In the third case, which occurred at the height of the epidemic, a healthy woman of 26 felt indisposed one morning and complained of headache. At mid-day she was seized with great weakness, became paralysed, sank into coma, and died the same evening. The only lesions found were a massive haemorrhage on

the surface of the cerebrum, and a fairly large haemorrhage in the white matter of the mid-brain. None of the vessels showed any evidence of atheroma or syphilitic change. One would not have felt justified in making a tentative diagnosis in this case had it not been that Buzzard and Greenfield had pointed out that massive haemorrhage may be the principal lesion of encephalitis. In the cases which they cite there were other evidences of encephalitis, but in our patient the attack may have fallen so heavily upon the vessels that death from haemorrhage supervened before there was time for the development of any further lesions.

Parenchymatous changes were less constant than the interstitial ones, and were similar in character to those described by other writers. They varied from such minor changes in the cells of the cranial nuclei as pigmentation, loss of the Nissl substance, and eccentricity of the nucleus, to profound degeneration and even disintegration. Neuronophagia is described by some writers as of frequent occurrence, but only very occasionally did we find it to be at all marked.

In seven cases, one of whom was only 23 years of age, amyloid bodies were found in various parts of the brain, namely, the cerebral cortex, basal ganglia, mesencephalon, pons, medulla, and in the spinal cord. As a rule they were confined to one region. Most numerous at the surface, around the aqueduct, and under the floor of the fourth ventricle, they were found in every part of the white and grey matter of the brain and in the posterior columns of the cord.

These bodies stained dark blue with thionin, a paler blue with haematoxylin, bluey-black with iodine, and not at all with Van Gieson. They were homogeneous, spherical, several times the diameter of a red blood corpuscle, and showed a darkly staining centre, but nothing resembling a nucleus. In some a concentric structure could be detected, resembling that of the corpora amylacea found elsewhere.

Such bodies are not infrequently found in the brain of the aged, but their occurrence in seven out of sixteen cases, many of them quite young, suggests that they may be degenerative products bearing some relation to encephalitis. Bassoe and Hassin (12) found spherical bodies in the cord of a case of lethargic encephalitis, but they differed in their staining reactions from those just described. Henrietta Calhoun (13) describes blue-staining homogeneous bodies in the brain of one case; these were confined entirely to the walls of the blood-vessels.

*Second epidemic.* Post-mortem examinations were made in nine of the cases of the second epidemic. On the whole, as was only to be expected, the lesions were very similar to those already observed three years previously. There were the same great congestion, thrombosis, and haemorrhage, the same perivascular infiltration, the same degeneration of nerve-cells. As before, perivascular infiltration was occasionally absent, or could only be detected after prolonged search.

Lesions were most frequent just under the floor of the fourth ventricle in the region of the nucleus of the seventh nerve. The mid-brain did not show vascular lesions as frequently as in the first epidemic, but degenerative changes

in the cells of the third nucleus were present in about 50 per cent. of the cases.

The most interesting lesions were those of the basal ganglia. In every case separate blocks were made of the caudate nucleus, the putamen, the globus pallidus, and the optic thalamus.

As the pains, which formed so prominent a feature of the epidemic, were very possibly central in origin, a careful examination was made of the thalamus on both sides. Unfortunately, most of the cases which came to autopsy had no definite localized pains. In one case, however, in which there was very severe pain in the arm, we found marked lesions (perivascular collars and thrombosis) in the thalamus, but none in the corpus striatum.

The corpus striatum was the centre of interest, as it was thought that the distribution of the lesions might explain some of the motor phenomena. Here again we were unfortunate in failing to obtain autopsies on the cases which showed the most striking motor manifestations. From a study of the limited material at our disposal it may be said that in the second epidemic the lesions were distributed fairly evenly between the neostriatum and the paleostriatum. The globus pallidus showed lesions in six instances, the putamen in seven, and the caudate nucleus in three. Of the six cases in which the globus pallidus was involved, in two the lesions were confined to that part of the corpus striatum, and in four they were also present in the neostriatum. In three cases the neostriatum alone was involved. In one of the cases in which the lesions were confined to the globus pallidus there was a complete absence of hyperkinesis.

The calcification which is described in the next section was found four times in the globus pallidus; three times in the putamen, and not at all in the caudate nucleus. In only one case was it found in both the putamen and globus pallidus.

Special interest was aroused by three lesions which will be considered separately; these are calcification of the vessels, amyloid bodies, and extreme dilatation of the vessels.

*Calcification.* In the third case which we examined we noticed peculiar bluish masses in the brain substance not unlike colonies of actinomyces, the exact significance of which we were at first at a loss to explain. It was soon noticed that the same material, staining dark blue with haematoxylin, was present in the wall of some of the blood-vessels, and it was then suspected that we were dealing with deposits of lime salts. The truth of this explanation was brought home forcibly when we discovered a series of notches in the sectioning razor.

The lime was found in three positions; in their order of frequency these were: (1) the wall of the vessel, (2) the interior of the vessel, and (3) the brain substance. It was present in six out of the nine cases, and only in the lenticular nucleus, chiefly the globus pallidus, but occasionally the putamen.

The calcified vessels were small arterioles with a distinct muscular wall. The capillaries were not involved. The lime in the vessel wall was confined as a rule to the middle and outer coats. Sometimes a calcareous ring would extend

completely round the vessel, but usually there was only a patch at one part of the circumference. No degeneration, atheromatous or otherwise, which might precede the deposition of lime could be made out in the uncalcified vessels. In those cases where the lime lay in the lumen of the vessel it had apparently broken away from the inner coat, for in an occasional vessel a thin deposit could be seen lying along and obscuring the endothelial lining. This deposit was apparently within the tunica intima, and was definitely limited by the internal elastic lamina. In one case there was calcification both of the outer and inner coats.

In haematoxylin and eosin specimens there was a remarkable resemblance between the calcareous deposits and the amyloid bodies about to be described. As the amyloid bodies were present in great abundance around the calcified vessels, one was led to wonder if the two lesions might both be expressions of the same pathological process.

It might be thought that the calcification was a senile phenomenon, such as is seen in the larger arteries in old age. That this was not the case is at once evident from a consideration of the ages of the patients, which were 19, 21, 33, 34, 41, and 60. Moreover, in none of the cases was there any atheroma or calcification of the large arteries at the base of the brain.

We have since had a sporadic case of encephalitis, which is in many ways the most remarkable of the series. The patient was a girl only 17 years of age, and she had been ill for only two days, and yet there were numerous deposits which we took to be lime salts in the vessels of the lenticular nucleus.

The deposits of lime salts are not comparable with those which may occur in old inflammatory lesions, for all of our cases were quite acute. The longest duration was four weeks, and in two cases the illness lasted only two and four days respectively. The process is therefore an acute calcification, and may be compared with the acute calcification of the epithelial cells of the renal tubules which follows corrosive sublimate poisoning. Herzog (14) observed similar calcium deposits in the wall of the small vessels of the brain in from two to eleven days after poisoning by coal gas.

The fact that calcification was found in patients only 17 and 21 years of age, after an illness of only two and four days respectively, raises another question. Is it not possible that the morbid process may have been going on for some time before any clinical symptoms appeared? And if this is so in one case, may it not be true for others? In examining a series of specimens of epidemic encephalitis one is struck by the fact that the lesions are more numerous than the symptoms. There may be well-marked vascular lesions around the nucleus of the seventh nerve without any facial paralysis. In the same way lesions of a non-suppurative encephalitis in more or less silent areas of the brain may pass unnoticed. This assumption that lesions may be present for some time before they announce their presence by giving rise to symptoms may account for the extraordinarily early appearance of calcification in some of our cases.

The question of calcification of the cerebral vessels is fully discussed by



McAlpine (15) in a recent paper which appeared after my own work was completed. His findings are very similar. In every one of six cases of encephalitis lethargica calcification in the lenticular nucleus was found, confined, however, to the anterior part of the globus pallidus. One patient was a child only 7 years old. In one case fat-like globules were present, some of which appeared to be becoming converted into lime. These globules, however, were not soluble in fat solvents.

Deposits of lime salts have been described by Buzzard and Greenfield as occurring in the vessel wall and in the perivascular haemorrhages in one of their cases of encephalitis. Dürck (16) observed marked calcification in 12 cases, the duration of the disease varying from eight days to five weeks. The lime salts occurred as free flakes in the brain substance as well as deposits in the vessel walls.

The question arises as to whether we are justified in regarding the process as one of calcification. Treatment of our sections with 5 per cent. nitric acid resulted in the disappearance of the greater part of the deposit; after two days only a faint indication of it could be detected. Weimann, who has made a careful chemical study of these deposits, found that they gave a positive iron reaction. Da Fano (17) summarizes our knowledge of the subject, but he is of the opinion that the term calcification has been loosely employed, and that the chemical composition of the deposits is by no means certain.

*Amyloid bodies.* Reference has already been made to the occurrence of amyloid bodies in 7 out of 16 cases in the first epidemic. They were found chiefly under the ependyma of the fourth ventricle and around the aqueduct of Sylvius, but were by no means confined to these regions.

In the second epidemic they were found in six out of nine cases. The respective ages of the patients were 19, 21, 33, 34, 41, and 60. Although similar in appearance to those formerly studied the distribution was different. They bore no relation to the ependyma, but bore a very marked relation to the dilated vessels, being clustered in large numbers around these structures and distributed very sparsely elsewhere. Moreover, the association with calcification was remarkably constant. Not only was calcification present in all the brains in which the amyloid bodies were found, but the bodies were usually confined to the same part of the brain as the lime salts.

The exact nature of the amyloid bodies and their mode of formation can at present be only a matter for conjecture. They are apparently formed as a result of a degeneration of the neuroglia, that degeneration probably taking the form of inflammatory softening consequent upon the action of the encephalitic virus. But why should they stain in a somewhat similar manner to the calcium deposits, why should they be grouped particularly around the calcified vessels, and above all, why should they so frequently present a curious concentric arrangement as if made up of a series of rings?

The analogy of the behaviour of colloids in chemistry and in geology may permit one to suggest the following explanation: When a solution of a salt such as silver nitrate is brought in contact with a colloid gel like gelatine to



which potassium bichromate has been added, a process of rhythmic precipitation sets in, and a succession of coloured rings are laid down, produced by the union of the bichromate with the silver salt as it gradually penetrates the gel, which acts as a semipermeable membrane. Calcium salts in solution have a similar power of producing rhythmic precipitation in a gel. Liesegang (18) has indicated that many geological substances which are characterized by the presence of concentric rings, as for instance the agate, are probably formed in this way. The rings so characteristic of urinary and biliary calculi may also be formed by the gradual action of an electrolyte upon a mass of colloid material. If small areas of neuroglial degeneration occurring as the result of the encephalitic toxin are clustered around a vessel, in the wall of which calcium salts are being deposited, may not the calcium-laden fluid gradually permeate the colloidal mass of softened brain tissue and bring about the phenomenon of rhythmic precipitation? This would explain the presence of the concentric rings, the similar staining shown by the amyloid bodies and the deposits of lime, and the relation of the bodies to the calcareous vessels. It would be interesting to estimate the blood calcium in any future cases of encephalitis which may occur.

Observations on the behaviour of the amyloid bodies towards decalcifying agents such as nitric acid confirmed the impression that these bodies consist largely of calcium salts. Sections were treated with 5 per cent. nitric acid for varying periods, and it was found that the amyloid bodies behaved in the same way as the lime in the vessel wall. After two days the lime in the wall could only faintly be made out, and the amyloid bodies had very largely faded away, only a central nucleus staining at all darkly. The rings in the peripheral part were very much more distinct than in the untreated specimen.

*Extreme dilatation of the vessels.* A moderate degree of vascular dilatation in various parts of the brain is a constant finding in encephalitis. In a few of our cases, however, a very different condition was observed. When the basal ganglia were sectioned, numerous large spaces from 2 to 3 mm. in diameter were seen in the posterior part of the lenticular nucleus, involving both the putamen and the globus pallidus. In the two cases in which the lesion was so marked as to be readily seen with the naked eye, the ages of the patients were 19 and 33.

The microscopic picture was that of a cluster of huge spaces, two or three of which were sufficient to occupy the entire lower-power field of the microscope.

The centre of the space was usually occupied by a greatly distended thin-walled blood-vessel, but in some instances this appeared to have dropped out. Although a few of the spaces were quite empty, most of them were occupied by large collections of serum, with here and there a few mononuclear cells. In the wall of some of the spaces were large numbers of amyloid bodies; in others none were to be seen. Fairly large spaces containing blood-vessels were seen in other brains, but these two were altogether in a class by themselves.

The cause of the spaces can only be a matter of speculation. In some respects they resemble the spaces sometimes seen in the basal ganglia in the brain in old age, the 'lacunae of cerebral disintegration', which are evidently the

result of insufficient nourishment of the brain substance due to an arterio-sclerotic condition of the vessels. On the other hand, the fact that they contain blood-vessels, and in many cases large quantities of serum, would suggest that they may be the result of great vascular dilatation coupled with a condition of extreme local perivascular oedema. At the same time the possibility that the condition may be nothing more than an artifact must not be overlooked.

*Summary.*

The clinical features of two epidemics of encephalitis lethargica in Winnipeg during the winters of 1919-20 and 1922-23 respectively were in the first a somnolent type, in the second excited. The different forms of pathological lesions in the brain are described. Evidence is adduced to prove that at least the greater portion of the hardening in the arteries of the basal ganglia is due to calcification.

# REFERENCES.

1. Hall, A. J., 'Encephalitis Lethargica', *Lancet*, Lond., 1923, i. 731.
2. Levaditi, Harvier, and Nicolau, 'Experimental Study on Encephalitis', *Ann. de l'Inst. Pasteur*, Paris, 1922, xxxvi. 63.
3. Kennedy, F., Davis, T. K., and Hyslop, G. H., 'An Additional Contribution to the Symptomatology of Epidemic Encephalitis', *Arch. Neurol. and Psychiat.*, Chicago, 1922, viii. 40.
4. Tilney, F., and Riley, H. A., *Form and Functions of the Central Nervous System*, Lond., 1921.
5. Anderson, Grace H., 'The Sequelae of Epidemic Encephalitis', *Quart. Journ. Med.*, Oxford, 1922-23, xvi. 173.
6. Schaller, W. F., and Oliver, J., 'Chronic Epidemic Encephalitis', *Arch. Neurol. and Psychiat.*, Chicago, 1922, viii. 1.
7. Bassoe, P., 'Discussion on Paper by E. L. Hunt', *Journ. Amer. Med. Assoc.*, Chicago, 1923, lxxxi. 1355.
8. Leiner, J. H., 'Spontaneous Cure of a Case of Epidemic Encephalitis following an Attack of Pneumonia', *ibid.*, Chicago, 1923, lxxxi. 1284.
9. Buzzard, E. F., and Greenfield, J. G., 'Lethargic Encephalitis: its Sequelae and Morbid Anatomy', *Brain*, Lond., 1919, xlii. 305.
10. Marinesco, G., 'Lethargic Encephalitis', *Bull. Acad. de méd.*, Paris, 1918, 3<sup>e</sup> sér., lxxx. 411.
11. Boyd, W., 'Epidemic Encephalitis: a Study of Seventy-five Cases with Sixteen Autopsies', *Annals of Medicine*, Hagerstown, Md., 1920, i. 195.
12. Bassoe, P., and Hassin, G. B., 'A Contribution to the Histopathology of Epidemic Lethargic Encephalitis', *Arch. Neurol. and Psychiat.*, Chicago, 1919, ii. 24.
13. Calhoun, Henrietta A., 'Histopathology of the Brain and Spinal Cord in a Case presenting a Postinfluenzal Lethargic Encephalitis Syndrome', *ibid.*, Chicago, 1920, iii. 1.
14. Herzog, *Münch. med. Woch.*, 1920, lxvii. 558. (Quoted by Hall.)
15. McAlpine, D., 'The Pathology of the Parkinsonian Syndrome following Encephalitis Lethargica, with a Note on the Occurrence of Calcification in this Disease', *Brain*, Lond., 1923, xvi. 255.
16. Dürck, E., 'Über die Verkalkung von Hirngefäßen bei der akuten Encephalitis Lethargica', *Ztschr. f. d. ges. Neurol. u. Psychiat.*, Berlin, 1921, Orig. lxxii. 175.
17. Da Fano, C., 'The Histopathology of Epidemic Encephalitis', *Medical Science*, Oxford, 1924, x. 3.
18. Liesegang, R. E., *Geologische Diffusionen*, Dresden, 1913.

# DESCRIPTION OF PLATES.

PLATE 6, FIG. 1. Deposit of lime salts in the wall of a vessel in the lenticular nucleus. The patient had only been ill for four days.

FIG. 2. Deposits of lime salts in the lenticular nucleus, one in the neighbourhood of a vessel, the other in the brain substance.

PLATE 7, FIG. 3. Calcification of a vessel wall with a mass of lime salts in the lumen of the vessel. Numerous amyloid bodies in the neighbourhood of the vessel.



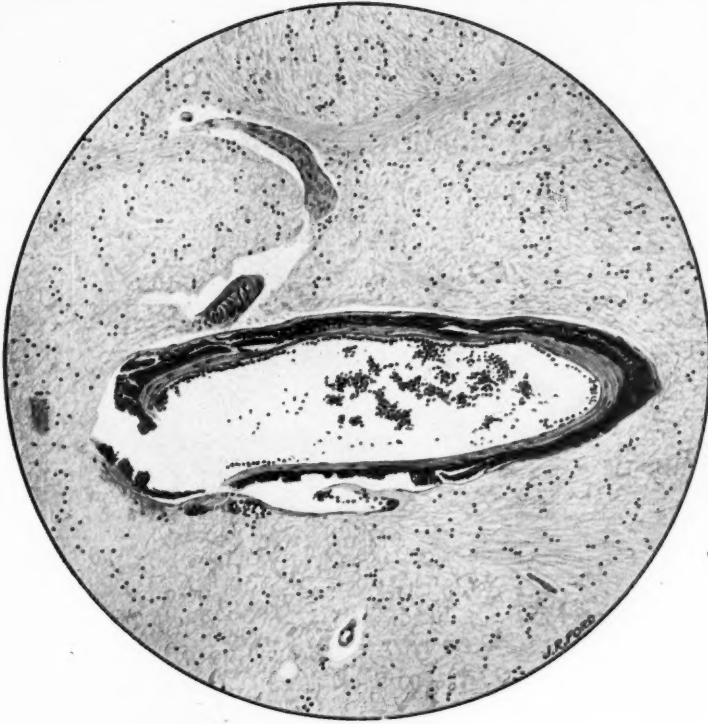


FIG. 1



FIG. 2

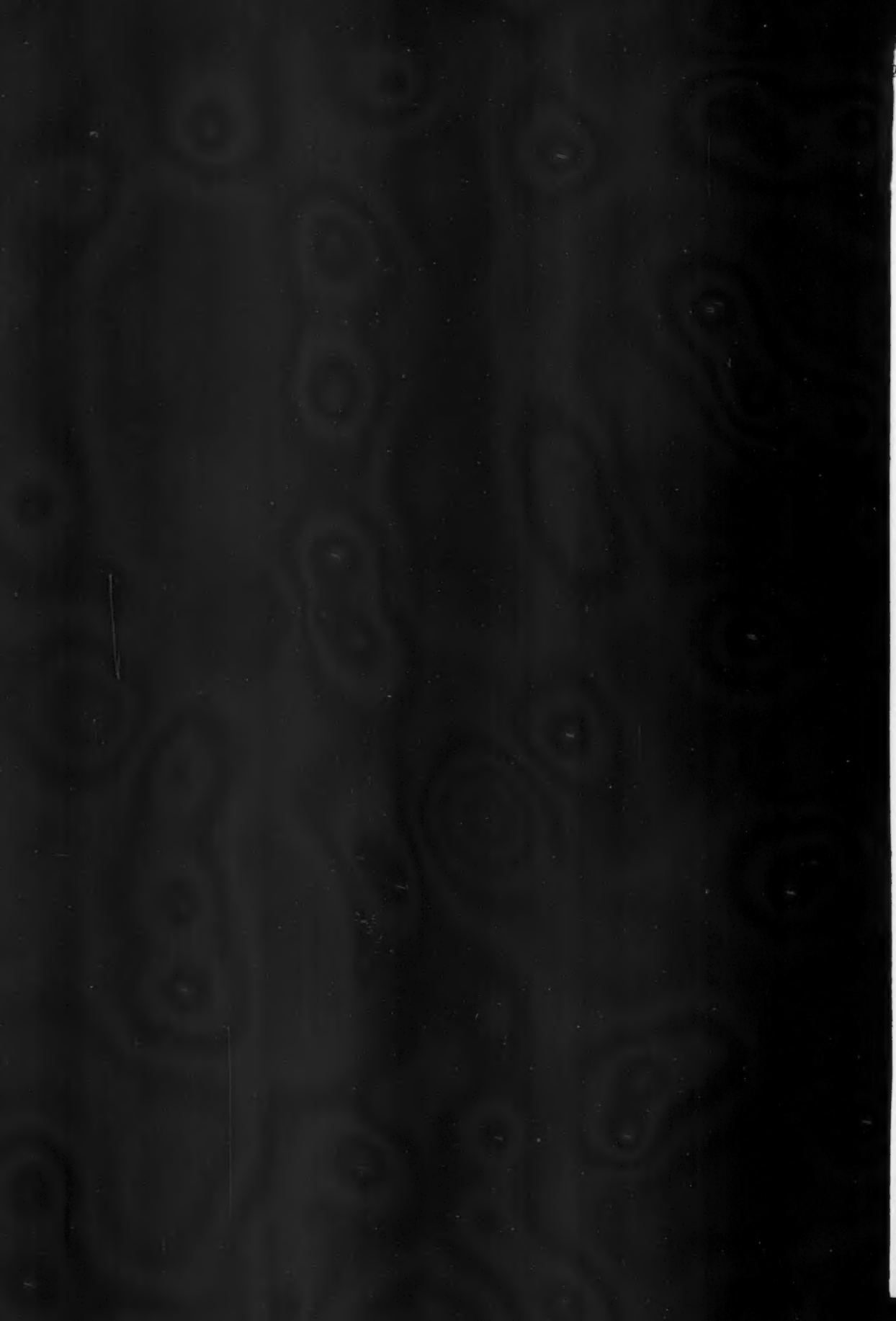






FIG. 3



## THE SUGAR CONTENT OF THE BLOOD IN NORMAL AND UNDER-NOURISHED CHILDREN, AND THE EFFECT OF FAT ON THE ABSORPTION OF CARBOHYDRATE<sup>1</sup>

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### *Introduction.*

THE cause of infantile atrophy has been studied from almost every angle. Within recent years the tendency has been to attribute it to intolerance of the organism to one or other of the proximate principles of the food. In some quarters it has been suggested that inability to digest or absorb protein or fat might be the underlying error, and much work has been done to find support for such a contention. The recent researches of Hutchison and Fleming (1, 2, 3), however, are distinctly against this explanation. By means of balance experiments Hutchison (1, 3) demonstrated that in atrophy the digestion and absorption of fat and protein are as efficient as in health, and Fleming (2, 3), from a study of the respiratory quotient and basal metabolism, concluded that in the marantic infant fats and carbohydrates are burned normally. Owing to the fact that the end-products resulting from the digestion and combustion of fat and protein can be detected, it is possible not only to determine the amount of these food-stuffs absorbed, but also the rate and extent of their oxidation. In the case of carbohydrate, however, it is quite different. It is no doubt possible from a study of the respiratory quotient to decide if carbohydrate after absorption is being oxidized normally, but, from the nature of the end-products ( $\text{CO}_2$ , lactic acid, and water) resulting from intestinal fermentation, it is quite impossible to estimate what proportion of the carbohydrate ingested is absorbed. In short, a balance experiment, i.e. carbohydrate ingested balanced against carbohydrate or its end-products excreted, cannot be carried out.

It was thought, however, that by studying the blood-sugar content some light might be thrown on the question of absorption and metabolism of carbohydrate, and, in consequence, the fasting blood-sugar content of healthy and atrophic infants were compared, as also the blood-sugar curves following the ingestion of a given amount of glucose.

<sup>1</sup> Received August 19, 1924.

*Method.*

Maclean's (4) method of estimating the blood-sugar was employed throughout the investigation. This method has the advantage of requiring only a very small quantity of blood (0.2 c.c.), an amount which can easily be obtained even in the smallest infant from the capillaries of the thumb. As, however, glycolysis is very active subsequent to the withdrawal of the blood the estimations must be carried out at once. I have found that after the sample of blood has stood for two hours at room temperature the sugar may be reduced as much as 30 per cent. In the following instances (Table I) two samples of blood were taken synchronously from the one patient: in one sample the sugar was estimated immediately after withdrawal, while the other was allowed to stand for at least two hours before the determination of the sugar content.

TABLE I.

Case 1.	.	.	.	Blood-sugar	.	.	.	12 p.m. = 0.100 %
				"	.	.	.	2.30 p.m. = 0.087 %
Case 2.	.	.	.	"	.	.	.	2 p.m. = 0.098 %
				"	.	.	.	4 p.m. = 0.068 %
Case 3.	.	.	.	"	.	.	.	2 p.m. = 0.081 %
				"	.	.	.	4 p.m. = 0.062 %

It was shown by Jacobsen (5) in 1913 that the most important factor which influences the sugar content of the blood at any particular moment is the ingestion of food. Consequently, it is essential for the obtaining of comparable results that the blood be withdrawn after a fast of sufficient duration to eliminate this factor, and, in my experience, a fast of three to four hours is sufficient for this purpose. The dose of glucose to provoke a rise was given immediately after the withdrawal of the first sample of blood, and an amount equal to 1 grm. glucose per kilo of expected weight was always found satisfactory. The glucose was dissolved in the requisite amount of water to make up a feed of sufficient quantity for the age of the child. The subsequent estimations were carried out at half-hourly intervals until the blood-sugar had again fallen to the fasting level.

From time to time the accuracy of the solutions employed in the estimations was checked by treating a 0.1 per cent. solution of pure glucose exactly as the blood filtrate.

A certain number of observations (see Table II) were made on the relationship between the percentage of cells, as determined by the haematocrite, and the percentage of sugar in the whole blood, because some workers, e.g. Graham (6) and Falta (7), have raised the question of the distribution of the sugar, and maintain that an accurate estimation of sugar content cannot be made without correcting for the variations between volume of cells and volume of plasma. These observations, however, do not show that this is a question of any significance.

TABLE II. *Blood-sugar Content in Relation to Volume of Cells  
(by Haematocrite)*

Name.	Percentage of Cells.	Percentage of Blood-sugar.
G. A.	40	0.100
O. C.	31	0.075
N. McK.	37	0.100
E. F.	45	0.085
H. McC.	43	0.080
A. J.	44	0.081
S. McL.	38	0.100
J. R.	40	0.092
T. McG.	40	0.093
M. C.	35	0.081
J. McV.	40	0.085
C. B.	37	0.065
C. M.	40	0.087
C. R.	38	0.087
E. C.	37	0.087
J. H.	45	0.100
R. H.	37	0.068
F. D.	40	0.081
M. C.	38	0.100
D. McK.	37	0.100

A. *The Fasting Blood-sugar Content.*

1. *In normal children.* Very different are the figures given by previous workers as to the normal fasting blood-sugar level in infancy, but as the following summary (Table III) reveals, this may be accounted for by the different methods of estimation employed.

TABLE III. *Fasting Blood-sugar Content obtained by different Workers  
in Normal Children.*

Author.	Date.	Age of Children.	Method employed.	Blood-sugar Content.	Mean Blood-sugar Content.
				%	%
Cobliner (8)	1911	9-21 days	Moeckel-Frank	0.076-0.098	0.085
Cobliner (8)	"	1-12 months	"	0.09-0.15	0.119
Götzky (9)	1913	Infants	Bang	—	0.077
Götzky (9)	"	2-14 years	"	—	0.105
Mogwitz (10)	1914	4-13 months	Bang	0.07-0.11	—
Mogwitz (10)	"	7 hours-8 weeks	"	0.07-0.103	—
Bergmark (11)	1914	Children	Bang	0.08-0.09	—
Bass (12)	1915	2-14 years	Lewis-Benedict	0.072-0.113	0.091
Cannata (13)	1917	First 24 hours	Lewis-Benedict	0.074-0.10	—
Chapin and Myers (14)	1919	Children	Lewis-Benedict	Slightly lower than in adults, which is 0.09- 0.12	—
Sedgwick and Ziegler (15)	1920	3-43 days	Folin	0.07-0.11	—
Lucas et alia (16)	1921	Few hours to 14 days	Folin	0.052-0.093	—
Spence (17)	1921	Under 3 years	Maclean	—	0.098
Guy (18)	1921	Under 1 year	Lewis-Benedict	0.06-0.09	0.068
Nystén (19)	1921	Under 1 month	Bang	—	0.101
Nystén (19)	"	1-12 months	"	—	0.123

As only very few estimations in infancy by Maclean's method were available, I found it necessary to establish for myself the normal level, and for this purpose selected thirty-five normal children, whose ages ranged from a few hours to one year. The results are graphically represented in Chart I, which shows the blood-sugar content according to the age of the child.

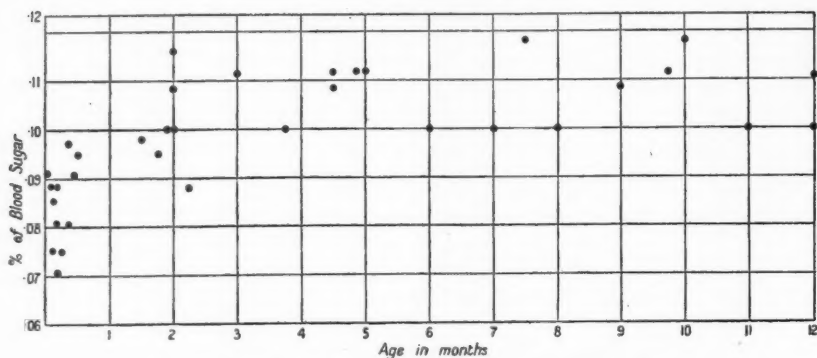


CHART I. Normal blood-sugar content according to age.

*Variation with age.* The most striking feature in the above series of estimations is the influence of age, a distinctly lower reading being obtained in children under two weeks old. In the children of two weeks or less the fasting blood-sugar level ranged from 0.072 per cent. to 0.097 per cent. with an average of 0.087 per cent., while in the children older than six weeks the sugar content varied between 0.086 per cent. and 0.116 per cent., the average being 0.106 per cent. As I have not had an opportunity of examining normal children between the ages of two and six weeks it is impossible to say exactly at what age the latter higher level is reached and whether it is a sudden or a gradual transition, but from the trend of the distribution of the findings in the children under two weeks of age it would seem as if the transition was a gradual one.

Previous workers have already noted a variation in the sugar content with the age of the child. Cobliner (8), in 1911, found that the normal infant has a slightly higher blood-sugar than the adult, except during the first month of life, when it is lower, a mean of 0.085 per cent. being obtained in children under one month as compared with a mean of 0.119 per cent. in children from 1 to 12 months of age. This low blood-sugar in the very young was confirmed two years later by Götzky (9) and still later by Nystén (19). Lucas et alia (16) in their investigations on the blood-sugar in the new-born found a steady increase as age advanced from a few hours to fourteen days after birth. Sedgwick and Ziegler (15) also investigated a series of children varying in age between three and forty-three days and found that the blood-sugar rose from 0.07 per cent. to 0.11 per cent. Guy (18), on the contrary, states that there is no variation with age, but on reviewing her results I find that she made no estimations in children under one month.



2. *In disease.* Previous workers have found that certain pathological conditions do influence the blood-sugar content, and in Table IV I have summarized the published results which have a bearing on the present discussion. It will be seen from this table that although the findings are not always in agreement there is, on the whole, a decrease in the blood-sugar in all cases of atrophy or decomposition and in dyspepsia, and an increase as a rule in enteritis.

TABLE IV. *Fasting Blood-sugar Content in Certain Pathological Conditions of various Authors.*

Author.	Disease.	No Change in Blood- sugar.	Increase.	Decrease.	Blood- sugar Content.
					%
Cobliner (8)	Atrophy	—	—	+	0.04-0.07
Guy (18)	Atrophy	—	—	+	0.06
Nystén (19)	Atrophy	—	—	+	0.114-0.115
Cobliner (8)	Decomposition	—	—	+	0.04-0.135
Chapin and Myer (14)	Malnutrition with acidosis	—	—	+	0.08-0.09
Nystén (19)	Dyspepsia	—	—	+	0.114-0.158
Guy (18)	Vomiting	—	—	+	0.037-0.059
Cobliner (8)	Dyspepsia	+	—	—	0.094-0.13
Götzky (9)	Enteritis	—	+	—	—
Mogwitz (10)	Enteritis	—	+	—	—
Nystén (19)	Intoxication	—	+	—	0.137-0.198
Cobliner (8)	Intoxication	+	—	—	0.11-0.123
Chapin and Myer (14)	Intoxication	+	—	—	0.08-0.11

(a) *Malnutrition.* Under this heading I have classified all children who were less than 80 per cent. of their expected weight for their age, irrespective of the cause of the emaciation, except that no case in which there was diarrhoea or vomiting has been included. There is no doubt, of course, that both vomiting and diarrhoea will bring about malnutrition, but as this is apparently due in great part to simple loss of food-stuffs the cases which gave such a history have been classified apart.

Thirty-two undernourished children, all over one month old, were examined. From Chart II, in which the fasting blood-sugar content has been plotted in relation to the percentage of expected weight, and thus to the relative state of nutrition, it is seen that not only is there a lower fasting blood-sugar level in malnutrition, but that the level rises steadily as the child approaches the normal state of nutrition for its age. It would thus seem that the blood-sugar level bears a definite relationship to the degree of wasting. In the child of less than 50 per cent. of its expected weight the fasting blood-sugar varied between 0.072 per cent. and 0.081 per cent. with an average reading of 0.077 per cent.; in the child of 50 per cent. to 80 per cent. of its expected weight the blood-sugar varied between 0.081 per cent. and 0.116 per cent., with an average of 0.091 per cent.; whereas in the child of 80 per cent. or more of its expected weight the average blood-sugar was 0.106 per cent., with a maximum of 0.118 per cent. and a minimum of 0.086 per cent.

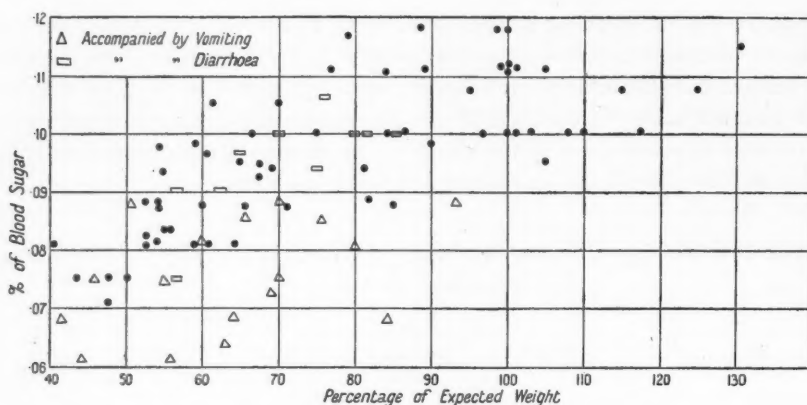


CHART II. Blood-sugar content according to state of nutrition.

In view of these results it seemed to me that it would be of interest to study the behaviour of the blood-sugar in marantic children during the period of recovery, and in consequence I selected four children, two of whom were treated in hospital and two as outdoor patients. To all sufficient food was being given, and all the children were gaining steadily in weight, and, as shown in Table V, there occurred in each instance a steady rise in the blood-sugar as the state of nutrition improved.

TABLE V. Increase of Blood-sugar as State of Nutrition improved.

	Age.	Date.	% Exp. Wt.	% Blood-sugar.
			%	%
Case 1	8/12 year	5.7.23	59	0.062
		13.9.23	59	0.068
		5.10.23	65	0.075
		10.12.23	75	0.098
Case 2	6/12 year	29.7.23	64	0.068
		15.8.23	69	0.075
		9.11.23	76	0.095
Case 3	8/12 year	19.11.23	47	0.075
		24.12.23	54	0.081
		5.2.24	61	0.094
Case 4	7/12 year	19.11.23	48	0.075
		20.12.23	52	0.075
		5.2.24	60	0.095

So far as I can find from a review of the literature no correlation has previously been made between the degree of glycaemia and the state of nutrition. Cobliner (8), however, does state that as the condition of the atrophic infant improves the percentage of blood-sugar increases, a fact confirmed later by Mogwitz (10).

(b) *Vomiting.* The cases accompanied by vomiting are represented on Chart II thus, Δ, and all reveal, quite irrespective of the state of nutrition, a very low blood-fasting level. That vomiting has a definite effect on the blood-sugar

has been shown by other workers, e.g. Guy (18) and Nystén (19), who found abnormally low-fasting levels in the presence of vomiting.

(c) *Diarrhoea*. As seen in Table IV some previous workers, e.g. Götzky (9) and Mogwitz (10), found an increase of blood-sugar in diarrhoea, while others again, e.g. Cobliner (8) and Chapin (14), obtained normal readings. In my cases, as seen from Chart II, where the children with diarrhoea are marked thus,  $\equiv$ , the blood-sugar level would appear to depend simply on the state of nutrition of the child. That the blood-sugar level in those cases bore no relationship to the degree of concentration of the blood was shown by taking synchronous haematocrite and blood-sugar readings (Table VI).

TABLE VI.

No.	% of Cells.	% of Blood-sugar.
1	38	0.100
2	40	0.100
3	31	0.100
4	35	0.105
5	40	0.096
6	35	0.075

#### B. Blood-sugar Tolerance Test.

1. *Normal infants*. The blood-sugar tolerance test was performed in ten normal children and the results obtained are given in Table VII. From these

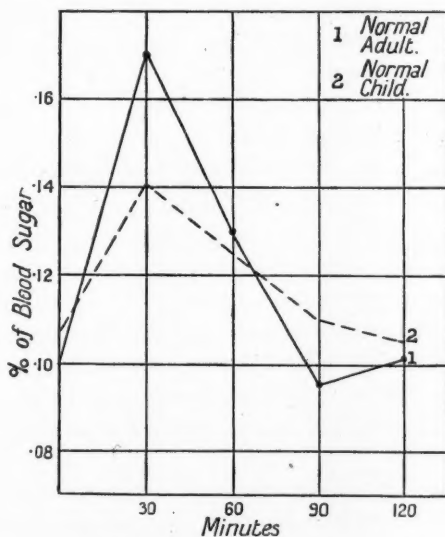


CHART III. Sugar tolerance curve.

and a composite curve represented in Chart III it is seen that after the ingestion of glucose the blood-sugar content does not rise to such a high level as in the case of the adult.

TABLE VII. *Blood-sugar Tolerance Test in Normal Children.*

No.	Age.	Wt.	Exp. Wt.	Fast-ing.	Blood-Sugar Content.			
					$\frac{1}{2}$ hour after Glucose.	1 hour after Glucose.	1½ hours after Glucose.	2 hours after Glucose.
		kg.	%	%	%	%	%	%
72	8/52 year	6.18	131	0.116	0.134	0.120	0.114	0.114
93	7/52 year	4.7	105	0.095	0.142	0.123	0.095	—
92	20/52 year	7.1	105	0.112	0.150	0.136	0.112	0.110
66	7/12 year	8.2	103	0.100	0.145	0.125	0.100	—
37	13 months	9.6	100	0.100	0.156	0.137	0.112	0.100
54	39/52 year	9.1	100	0.112	0.156	0.125	0.112	0.112
56	1 year	9.5	100	0.112	0.150	0.132	0.112	—
74	29/52 year	7.86	100	0.118	0.141	0.125	0.118	—
14	6½/52 year	3.8	90	0.098	0.106	0.120	0.106	0.098
29	9½/52 year	4.0	84	0.087	0.130	0.112	0.108	0.088
Mean				0.106	0.141	0.125	0.110	

2. *In disease.* The blood-sugar tolerance test was performed in fifty children admitted to hospital suffering from the following ailments :

11 cases of gastro-enteritis.

3 " " enteritis.

3 " " pyloric stenosis.

3 " " pylorospasm.

12 " " pulmonary infection.

8 " " marasmus.

6 " " incorrect feeding.

1 case of tetany.

1 " " congenital cystic kidney.

1 " " hydrocephalus.

1 " " congenital obliteration of the bile-ducts.

Although almost all the infants included in this group are less than 80 per cent. of their expected weight it will be seen that except in the three examples of pyloric stenosis and one child with congenital obliteration of the bile-ducts, the sugar tolerance test was within normal limits.

The three children with pyloric stenosis showed a delayed curve, the blood-sugar not rising to its height till 1-1½ hours after the ingestion of glucose. That there is delayed absorption in pyloric stenosis with its much-impaired gastric motility is not to be wondered at, as practically no sugar is absorbed from the stomach.

In the example of congenital obliteration of the bile-ducts the blood-sugar rose to its height in half an hour, but even 2½ hours after the glucose had been taken the blood-sugar was still well above the fasting level. In all likelihood this is to be accounted for by a cirrhotic condition of the liver, which we know interferes with the storage of glycogen and which is probably a constant sequel to obliteration of the bile-ducts.

TABLE VIII.

*Blood-sugar Tolerance Test in Under-nourished Infants.*

No.	Age.	Wt.	Exp. Wt.	Blood-sugar Content.					Diagnosis.
				Fasting.	30 mins. after Glucose.	60 mins. after Glucose.	90 mins. after Glucose.	120 mins. after Glucose.	
		kg.	%	%	%	%	%	%	
29	9/52	4	85	0.087	0.150	0.112	0.108	0.081	Gastro-enteritis
36	1 yr.	8	88	0.119	0.156	0.137	0.119	—	" "
78	11/52	4.2	77	0.112	0.187	0.129	0.125	0.112	" "
33	5/52	3.1	75	0.100	0.140	0.131	0.100	0.098	" "
41	45/52	6.4	67	0.096	0.156	0.131	0.096	—	" "
19	38/52	4.6	54	0.088	0.131	0.156	0.112	0.094	" "
17	15/52	4.1	71	0.106	0.137	0.144	0.118	0.106	" "
38	19/52	4.5	70	0.068	0.100	0.110	0.100	0.068	" "
88	2/52	3	65	0.107	0.182	0.114	0.118	0.112	" "
82	3/12	3.8	64	0.099	0.132	0.139	0.099	—	" "
23	42/52	5	56	0.062	0.112	0.131	0.062	0.068	" "
21	11/52	4.2	76	0.106	0.156	0.131	0.131	0.106	Enteritis
39	1 yr.	6.6	70	0.100	0.110	0.150	0.110	0.100	" "
89	13/12	5.1	57	0.092	0.129	0.154	0.100	0.098	" "
9	4/52	3.2	84	0.068	0.094	0.130	0.116	0.094	Pyloric stenosis
27	10/52	4.1	80	0.081	0.093	0.108	0.118	0.081	" "
87	5/12	3.6	51	0.089	0.017	0.113	0.132	0.104	" "
2	4/12	4.7	70	0.087	0.118	0.125	0.087	0.087	Pylorospasm
24	4/12	4	61	0.096	0.106	0.150	0.125	0.096	" "
1	4/12	3.6	55	0.075	0.143	0.112	0.075	—	" "
4	45/52	6	70	0.075	0.162	0.132	0.100	0.075	Br. pneumonia
13	10/52	3.5	66	0.087	0.100	0.118	0.081	0.087	Unresolved pneumonia
16	40/52	5.8	64	0.068	0.100	0.087	0.062	—	Br. pneumonia
6	14/12	4.1	46	0.075	0.162	0.112	0.075	—	Chronic pneumonia and endocarditis
83	6/52	2.6	60	0.082	0.134	0.127	0.100	0.082	Pemphigus and br. pneumonia
5	30/52	6	66	0.087	0.100	0.110	0.087	—	Br. pneumonia
43	46/52	4.9	54	0.087	0.131	0.108	0.108	0.098	" "
59	14/52	3.3	55	0.084	0.121	0.108	0.084	—	" "
18	20/52	2.7	40	0.081	0.119	0.106	0.110	0.087	Tub. lung
42	10/12	6.4	70	0.106	0.150	0.136	0.106	0.106	Br. pneumonia
8	10/12	7.2	80	0.100	0.141	0.130	0.106	—	" "
35	17/12	8	80	0.100	0.131	0.156	0.106	0.100	" "
45	6/12	4.8	63	0.064	0.100	0.131	0.064	—	Marasmus
25	9/52	3.4	69	0.074	0.094	0.131	0.106	0.078	" "
15	4/12	3.7	59	0.098	0.150	0.143	0.108	0.095	" "
84	9/12	4.5	54	0.097	0.115	0.104	0.098	—	" "
44	7/52	3.4	53	0.083	0.131	0.100	0.083	—	" "
17	9/52	2.6	53	0.081	0.140	0.156	0.131	0.081	" "
85	10/52	2.7	53	0.087	0.114	0.094	0.079	0.086	" "
28	15/52	2.5	43	0.075	0.100	0.098	0.068	0.075	" "
12	14/52	5.0	72	0.094	0.150	0.112	0.094	—	Incorrect feeding
7	5/12	4.2	61	0.081	0.106	0.094	0.081	—	" "
22	18/52	4.2	64	0.081	0.132	0.119	0.100	0.087	" "
26	5/52	2.4	60	0.087	0.100	0.118	0.081	0.087	" "
20	4/12	2.8	44	0.068	0.081	0.112	0.086	0.068	" "
40	14/52	2.5	41	0.068	0.137	0.094	0.068	—	" "
31	1 yr.	7.5	71	0.087	0.100	0.108	0.104	0.087	Tetany
3	7/52	6.7	84	0.100	0.137	0.131	0.089	0.100	Congenital cystic kidney
77	6/12	5.9	79	0.118	0.129	0.149	0.149	0.118	Hydrocephalus
80	8/52	3.1	65	0.095	0.177	0.134	0.120	0.118	Congenital biliary atresia

*Discussion.*

The first question which naturally arises from a consideration of the above findings is the cause of the hypoglycaemia met with in the severely under-nourished infant. There would seem to be two possibilities: (1) an insufficient supply of carbohydrate consequent either on defective intake or on defective absorption, and (2) a lessened need for sugar on account of the diminished amount of active metabolic tissue resulting from the emaciation.

It has usually been held that prolonged starvation, both in man and in animals, does not lead to a lowering of the blood-sugar, and Allen (20) states that 'the normal percentage of sugar in the blood is stubbornly maintained through prolonged starvation almost to death'. These findings refer, of course, to the adult, and also to complete starvation, and not to partial and chronic starvation, as must be the case in our material. Mogwitz (10) reports five children in whom a lowering of the blood-sugar did result from starvation. This author starved one infant for seventy-eight hours, giving only water and saccharine, and found that the blood-sugar, which was 0.09 per cent. three hours after the last milk feed, had fallen to 0.047 per cent. seventy-eight hours later.

The low figure found in the new-born would certainly support the idea of starvation, which we now believe is the cause of the so-called physiological loss in weight. The newly born seldom, if ever, get a sufficiency of nourishment. Not only does it take some time for lactation to be thoroughly established, but also the first milk (colostrum) is relatively poor in carbohydrate.

In the second place, the very low blood-sugar found in the cases with vomiting, where it is apparent that the child is not getting sufficient food, lends further support to the hypothesis of starvation. Nevertheless, it seems difficult to explain in this way the steady increase in the blood-sugar proportionate to the improvement in the state of nutrition. One would have thought that in the presence of ample food the blood-sugar would quickly reach the normal level. It is quite possible, and in fact not unlikely, that the children had been starved before the onset of the atrophy, and also before coming under observation, but at the time of the blood examination they had all been, for some days at least, on an ample diet. To some of the children, too, e. g. those observed during recovery and recorded in Table V, an ample supply of carbohydrate had been given; in one child this had been the case for as long a period as four months, and yet the blood-sugar had not returned to normal. As showing that the children had also been absorbing a sufficiency for their needs is the fact that during this time they were all steadily gaining in weight.

Is it, then, that this lowered blood-sugar is due to the call for a lessened amount of mobilized sugar because of the diminished amount of active metabolic tissue from wasting of muscle, &c.? With increased metabolism, as in fever, hyperthyroidism, and after exercise, a hyperglycaemia results, and it would therefore seem not improbable that in diminished metabolism, as undoubtedly occurs in emaciation, the reverse would be obtained.



The question of blood-volume in various states of nutrition should also be borne in mind. If there is, as Bakwin and Rivkin (21) state, a relative increase of blood volume in marasmus then the whole variation in the sugar content may be explained by simple dilution.

Though the blood-sugar tolerance tests do not show any abnormality except in pyloric stenosis and biliary atresia, one cannot thus definitely conclude that absorption is unimpaired, since several factors come into play. The curve obtained after ingestion of glucose is not merely an expression of the amount of glucose absorbed from the gut, but is influenced by the storage capacity of the liver, the glycogenolytic activity of the liver, and the amount of glycolysis in the tissues. If all these factors could be eliminated it would only require the addition of a few grammes of carbohydrate to the blood to raise its sugar content considerably.

#### *C. Effect of Fat on the Absorption of Carbohydrate.*

It is generally believed that infants, and especially marantic infants, often thrive better on a low fat and high carbohydrate diet than on one containing a low proportion of carbohydrate and a high proportion of fat, and the reason generally given has been the supposed difficulty of the organism to absorb fat. Hutchison (1), however, in a recent research on fat absorption in the normal and atrophic infant, could find no evidence in favour of such a contention, and showed that fat was equally well absorbed by the normal and atrophic infant.

Some years previously Rosenstern (22) had demonstrated by clinical experiments that when a child was not gaining weight on a high fat diet, increase in weight could be induced by the simple addition of sugar so long as no dyspeptic symptoms developed. He postulated that there was a minimal requirement of carbohydrate, a requirement which varied in different individuals, and which was quite irrespective of the caloric supply of the diet. It seemed, too, in view of the small amount of carbohydrate which it was necessary to add, and the great increase in weight which resulted, that the sugar exerts a catalytic effect.

But the possibility that in some way the fat may interfere with the absorption of sugar must also be borne in mind. This is a point which has been little considered. From the above results of the estimation of sugar tolerance it is seen that both in health and disease sugar is equally well absorbed. In these tests, however, sugar was administered alone, and it was felt that if the sugar was presented in association with fat, and especially large amounts of fat, as may occur in the child's diet, some defect in the absorption of sugar might be revealed. This seemed all the more likely in view of a metabolism study by Fleming (23) in a case of congenital obliteration of the bile-ducts, in which fat absorption was very defective, as evidenced by the dried faeces' fat content being 60 per cent. to 80 per cent. instead of the normal 30 per cent. to 40 per cent. Fleming found that a higher respiratory quotient was obtained when the child was given a fat-poor diet than when it was given a fat-rich

diet, and suggested impaired absorption of sugar through the greatly increased amount of unabsorbed fat residue in the gut as an explanation for the difference.

The method which I adopted for testing this hypothesis was the administration of diets containing similar amounts of carbohydrate but varying amounts of fat, and observing the behaviour of the blood-sugar curve under these varying conditions. The fasting blood-sugar was determined, and thereafter the blood-sugar curve on a diet of lactose and water and of lactose and milk containing different percentages of fat. The diets containing different amounts of fat, but with a constant lactose content, were administered for two to three days before determining the blood-sugar absorption curve. The amount of lactose in each feed was in an amount approximately equal to 1 gm. per kilo of expected body-weight. Maclean's method of estimating the blood-sugar was used throughout the experiment.

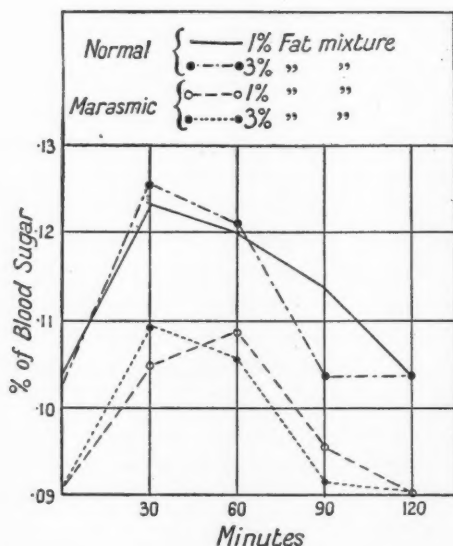


CHART IV. Average blood-sugar content after 1 per cent. and 3 per cent. fat milk mixtures.

Five normal and five marantic infants, all under 1 year of age, were chosen as subjects.

The results obtained from these experiments are given in Table IX, and composite curves are shown in Chart IV. From these it will be observed that the increased amount of fat apparently did not cause any interference with the absorption of carbohydrate in either the normal or the atrophic infant. We must, of course, assume in adjudicating these results that the blood-sugar content is really a gauge of the absorption of carbohydrate, but it should not be forgotten that hepatic efficiency and pancreatic efficiency, by influencing sugar storage, will also modify the amount of carbohydrate circulating in the blood.

TABLE IX.  
*Blood-sugar Content after Different Diet.<sup>1</sup>*

No.	Diet.	% Blood-sugar.						Condition.
		Fast- ing.	½ hour after Feed.	1 hour after Feed.	1½ hours after Feed.	2 hours after Feed.	2½ hours after Feed.	
		%	%	%	%	%	%	
1	200 c.c. H <sub>2</sub> O + 8.5 gm. lactose	0.108	0.136	0.125	0.112	0.106	—	Normal
	200 c.c. 1 % fat milk	0.100	0.131	0.118	0.125	0.118	0.106	
	200 c.c. 3 % fat milk	0.100	0.131	0.131	0.100	0.100	—	
2	210 c.c. H <sub>2</sub> O + 9 gm. lactose	0.100	0.112	0.106	0.100	0.098	—	Normal
	210 c.c. 1 % fat milk	0.100	0.106	0.098	0.100	0.106	—	
	210 c.c. 3 % fat milk	0.106	0.112	0.100	0.100	—	—	
3	150 c.c. H <sub>2</sub> O + 6.5 gm. lactose	0.112	0.132	0.108	0.116	0.112	—	Normal
	150 c.c. 1 % fat milk	0.112	0.125	0.131	0.116	0.108	—	
	150 c.c. 3 % fat milk	0.108	0.131	0.125	0.112	0.112	—	
4	180 c.c. H <sub>2</sub> O + 7.7 gm. lactose	0.100	0.125	0.112	0.106	0.112	0.106	Normal
	180 c.c. 1 % fat milk	0.108	0.125	0.131	0.125	0.100	—	
	180 c.c. 3 % fat milk	0.108	0.131	0.112	0.100	0.106	—	
5	210 c.c. H <sub>2</sub> O + 10 gm. lactose	0.100	0.140	0.131	0.125	0.100	0.100	Normal
	210 c.c. 1 % fat milk + 1 gm. lactose	0.100	0.131	0.125	0.108	0.100	—	
	210 c.c. 3 % fat milk + 1 gm. lactose	0.100	0.131	0.145	0.112	0.108	0.100	
6	210 c.c. H <sub>2</sub> O + 9 gm. lactose	0.087	0.100	0.098	0.100	0.087	0.087	Marantic
	210 c.c. 1 % fat milk	0.087	0.112	0.100	0.094	0.087	—	
	210 c.c. 3 % fat milk	0.087	0.112	0.100	0.076	0.087	—	
7	180 c.c. H <sub>2</sub> O + 7.2 gm. lactose	0.086	0.119	0.098	0.094	0.087	—	Marantic
	180 c.c. 1 % fat milk	0.086	0.100	0.108	0.098	0.086	—	
	180 c.c. 3 % fat milk	0.086	0.098	0.112	0.094	0.086	—	
8	180 c.c. H <sub>2</sub> O + 8.1 gm. lactose	0.081	0.100	0.112	0.098	0.081	—	Marantic
	180 c.c. 1 % fat milk + 1 gm. lactose	0.081	0.100	0.112	0.098	0.081	—	
	180 c.c. 3 % fat milk + 1 gm. lactose	0.081	0.112	0.100	0.094	0.081	—	
9	180 c.c. H <sub>2</sub> O + 8 gm. lactose	0.094	0.112	0.125	0.100	0.098	0.094	Marantic
	180 c.c. 1 % fat milk + 1 gm. lactose	0.098	0.108	0.112	0.094	0.098	—	
	180 c.c. 3 % fat milk + 1 gm. lactose	0.098	0.112	0.112	0.098	0.100	0.094	
10	165 c.c. H <sub>2</sub> O + 7 gm. lactose	0.100	0.100	0.112	0.108	0.100	—	Marantic
	165 c.c. 1 % fat milk	0.100	0.108	0.112	0.100	0.100	—	
	165 c.c. 3 % fat milk	0.098	0.112	0.108	0.100	0.100	—	

\* 100 c.c. whole milk has been found by repeated examinations to contain on an average 4.5 gm. of lactose.

TABLE X.

*Blood-sugar Content after 1 per cent. and 8 per cent. Fat Milk Mixtures.*

No.	Diet.	% Blood-sugar.						Condition.
		Fast- ing.	$\frac{1}{2}$ hour after Feed.	1 hour after Feed.	1 $\frac{1}{2}$ hours after Feed.	2 hours after Feed.	2 $\frac{1}{2}$ hours after Feed.	
11	210 c.c. 1% fat milk	0.106	0.110	0.112	0.100	0.100	—	} Normal
	210 c.c. 8% fat milk	0.100	0.112	0.108	0.100	0.100	—	
12	180 c.c. 1% fat milk	0.100	0.112	0.118	0.112	0.098	0.100	} Normal
	180 c.c. 8% fat milk	0.106	0.125	0.118	0.100	0.100	—	
13	150 c.c. 1% fat milk	0.112	0.134	0.125	0.112	0.112	—	} Normal
	150 c.c. 8% fat milk	0.112	0.125	0.125	0.108	0.112	—	
14	150 c.c. 1% fat milk + 1 grm. lactose	0.098	0.108	0.112	0.100	0.098	0.100	} Marantic
	150 c.c. 8% fat milk + 1 grm. lactose	0.098	0.112	0.100	0.094	0.094	—	
15	200 c.c. 1% fat milk	0.087	0.100	0.112	0.098	0.087	0.092	} Marantic
	200 c.c. 8% fat milk	0.087	0.112	0.100	0.094	0.087	—	
16	165 c.c. 1% fat milk	0.098	0.106	0.112	0.098	0.098	0.092	} Marantic
	165 c.c. 8% fat milk	0.098	0.112	0.108	0.100	0.094	—	

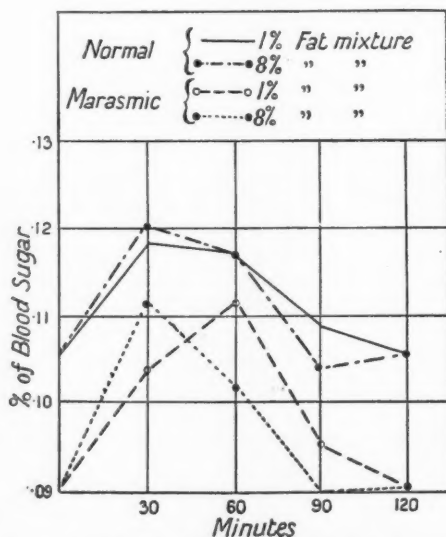


CHART V. Average blood-sugar content after 1 per cent. and 8 per cent. fat milk mixtures.

It is thus seen that although, as already shown, the blood-sugar level in atrophy is lower than in health, the rate and extent of rise and also the duration of rise in blood-sugar after ingestion are absolutely parallel in health and marasmus.

In view of the absence of any difference in the above findings it was decided to see the effect of greater variations in the fat content of the diet. Six children, three of whom were normal and three marantic, were given diets of 1 per cent. fat milk and 8 per cent. fat milk mixtures (the amount of carbohydrate being constant) and the absorption curves contrasted. The 8 per cent. fat milk mixtures were obtained by adding cream to undiluted milk, the amount of fat being calculated by means of the Werner-Schmidt process.

As seen from Table X and Chart V no delay in the absorption of sugar was obtained even when a diet containing as much as 8 per cent. fat was given; in fact, the curves show relatively a greater rise in the case of the marantic infants.

#### *Conclusions.*

1. The sugar content of the blood in normal infants up to two weeks of age varies between 0.072 per cent. and 0.097 per cent., and from six weeks up to one year from 0.086 per cent. to 0.116 per cent.

2. In the under-nourished infant the blood-sugar varies between 0.072 per cent. and 0.116 per cent., rising steadily as the percentage of expected weight increases.

3. Vomiting *per se* causes a marked diminution in the blood-sugar.

4. Diarrhoea does not seem to influence the blood-sugar level.

5. In infancy the sugar tolerance curve is lower than in the adult, but the curve is identical in the normal and under-nourished child.

6. A delayed rise in the blood-sugar was obtained in three cases of pyloric stenosis, while a delayed fall was found in one case of congenital obliteration of the bile-ducts.

7. So far as blood-sugar tolerance tests are concerned they supply no evidence that a high fat content in the diet interferes with the rate of absorption of the carbohydrate in the diet.

I wish to extend my sincerest thanks to Dr. Leonard Findlay, under whose guidance this work was performed. I am also much indebted to the Medical Research Council, by whom all expenses have been defrayed.

## REFERENCES.

1. Hutchison, *Quart. Journ. Med.*, Oxford, 1919-20, xiii. 277.
2. Fleming, *Glasgow Med. Journ.*, 1921, xvi. 337.
3. Fleming and Hutchison, *Quart. Journ. Med.*, Oxford, 1923-4, xvii. 337.
4. Maclean and de Wesselow, *ibid.*, Oxford, 1920-1, xiv. 103.
5. Jacobsen, *Biochem. Zeitsch.*, Berlin, 1913, lvi. 471.
6. Graham, *Lancet*, Lond., 1921, i. 951.
7. Falta, *Biochem. Zeitsch.*, Berlin, 1919, c. 148.
8. Cobliner, *Zeitsch. f. Kinderheilk.*, Berlin, 1910, i. 207.
9. Götzky, *ibid.*, Berlin, 1913, Orig. ix. 44.
10. Mogwitz, *Monatsch. f. Kinderheilk.*, Leipzig, 1914, Orig. xii. 569.
11. Bergmark, *Jahrb. f. Kinderheilk.*, Berlin, 1914, N. F. lxxx. 373.
12. Bass, *Amer. Journ. Dis. Child.*, Chicago, 1915, ix. 63.
13. Cannata, *Pediatrics*, Napoli, 1917, 2<sup>a</sup> ser. xxv. 513.
14. Chapin and Myers, *Amer. Journ. Dis. Child.*, Chicago, 1919, xviii. 555.
15. Sedgwick and Ziegler, *ibid.*, Chicago, 1920, xix. 429.
16. Lucas et alia, *ibid.*, Chicago, 1921, xxii. 525.
17. Spence, *Quart. Journ. Med.*, Oxford, 1920-1, xiv. 314.
18. Guy, *ibid.*, Oxford, 1921-2, xv. 9.
19. Nystén, *Acta Paediat.*, Upsala, 1921, i. 79.
20. Allen, D. M., *Glycosuria and Diabetes*, Oxford, 1914, 9.
21. Bakwin and Rivkin, *Amer. Journ. Dis. Child.*, Chicago, 1924, xxvii. 340.
22. Rosenstern, *Zeitsch. f. Kinderheilk.*, 1911, ii. 481.
23. Fleming, *Amer. Journ. Dis. Child.*, Chicago, 1922, xxiii. 66.



## THE GEOGRAPHICAL DISTRIBUTION OF EXOPHTHALMIC GOITRE IN THE BRITISH ISLES<sup>1</sup>

By J. M. H. CAMPBELL<sup>2</sup>

### *Introduction*

THE geographical distribution of goitre was recognized many centuries ago, and endemic areas in the Alps were described by Juvenal and Pliny, e. g. 'Quis tumidum guttur miratur in Alpibus', and 'Guttur homini tantum et suibus intumescit, aquarum quae potantur plerumque vitio'.

In the Middle Ages goitre was looked on as a more direct intervention of God, and there is more than one legend of wrongdoing where the curse delivered was that 'the children should be born cripples and the women goitrous'. Towards the end of the thirteenth century Marco Polo described it in the plateau of Central Asia.

One of the earliest and most important medical writings on the subject was by Paracelsus at the beginning of the seventeenth century. In *De generatione stultorum* he describes the endemic areas of goitre and gives the first accurate account of cretinism, discussing the relationship between the two. From then onwards the subject has been studied continuously, and in most European countries the local incidence is well known from the numbers of recruits for military service rejected for goitre in different parts of the country. The distribution in France has been described and the whole question discussed very fully by Baillarger (1).

The known facts about the distribution throughout the world have been summarized by Hirsch (2), so need not be referred to further. His book is a mine of information and I am much indebted to it.

Exophthalmic goitre was only described at the beginning of the last century, and there is not much knowledge about its geographical distribution. Berry says: 'Exophthalmic goitre is not an endemic disease. My own inquiries in many goitrous districts both in England and abroad point in the same direction and tend to show that exophthalmic goitre is rare in places where ordinary goitre is common, and certainly is often found in places where ordinary goitre is unknown' (3).

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<sup>2</sup> Working under the tenure of a Beit Memorial Fellowship, and previously under that of the Hilda and Ronald Poulton Fellowship at Guy's Hospital.

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On the other hand, Mackenzie says: 'Certain parts of Kent, Surrey, Wiltshire, and the Thames Valley have produced a relatively large proportion of the cases under my observation. In districts where ordinary goitre prevails, the exophthalmic form is more common than in other parts' (4).

McCarrison in a more recent work (5) says: 'We know little of the climatic or geographical distribution of exophthalmic goitre, of the influence of race, of season, of altitude, of its prevalence in town or country, or of its incidence among the rich and poor. It is stated to be more common at the sea-coast than inland, but this is an impression only. It is, however, very rare in regions where goitre is endemic. Amongst the indigenous inhabitants of goitrous tracts of the Himalayas I have seen comparatively few cases in ten years. It is said that this does not hold good of Switzerland or of the region of the Great Lakes of North America, but Bircher's experience in Switzerland is similar to mine in the Himalayas.'

With such differences of opinion about the relationship of endemic goitre and Graves's disease, and such a complete absence of information about the geographical distribution of the latter, it seemed worth collecting some statistical evidence. It is interesting that as long ago as 1870 Wilks (6) described a case of exophthalmic goitre in a man whose two brothers suffered from ordinary goitre. His picture is given and shows a typical case of Graves's disease with an unusually large thyroid. But this is not a very common combination. In a series of over 100 cases of exophthalmic goitre in Guy's Hospital more than 5 per cent. gave a history of one or more close relatives with the same disease, while a history of ordinary goitre was not common.

Although so much has been learnt in the last thirty years about exophthalmic goitre, its aetiology still remains obscure, and any facts about its local distribution may be of service in making this clearer—by correlating its incidence with the water-supply or its iodine content, with the soil or climate, or with other factors.

The sudden onset of Graves's disease after fright or other emotions makes the general question of its aetiology more interesting. Such psychological causes can only be the exciting stimulus when the underlying conditions are suitable. It is with the latter that this paper is concerned.

In 1921 some evidence was brought forward that there was a local distribution of Graves's disease in England and Wales (7). Corresponding figures for Scotland and Ireland have now been obtained, and the whole subject can be considered more fully.

### *Part I. Distribution of Exophthalmic Goitre.*

#### *Statistical Data.*

In the Registrar-Generals' annual reports the deaths from exophthalmic goitre are not tabulated under the various districts, but these figures have kindly been given me by the Registrar-Generals; for England and Wales for the seven

# GEOGRAPHICAL DISTRIBUTION OF EXOPHTHALMIC GOITRE 193

years 1913-19, for Scotland for the ten years 1911-20, and for Ireland for the ten years 1913-22.

In England and Wales separate figures were obtained for the county boroughs and the urban and rural districts. In most counties the incidence was higher in the rural than in the urban districts, but there was good general agreement between the figures for the two. This is shown in Table I. For this reason the urban and rural districts have been taken together throughout the paper, but the county boroughs have been separately considered and are not included with the figures given for the counties, although there is again a good deal of general agreement.

In Ireland and Scotland the populations are not large enough for such subdivision. In Ireland all towns, except Dublin and Belfast, are included with the county figures. In Scotland all towns are included with the county figures, but statistics for the seven largest burghs are also available. It is unfortunate that these statistics were not collected on an absolutely uniform system, and that they include the period of the war, but in spite of this certain definite conclusions can be drawn.

TABLE I. *Comparison of the Mortality from Exophthalmic Goitre in Rural and Urban Districts.*

County.	Rural District.	Urban District.
Durham	8.9	7.8
Cumberland	22.8	19.5
Lancashire	22.2	17.2
Yorks. (W. R.)	13.3	14.3
Somerset	23.4	16.0
Dorset	9.5	8.2
Suffolk	13.8	13.7
Essex	9.0	5.3

Figures are the number of deaths annually per million of population living. Only Northumberland, Leicester, and Bedford show much disagreement; Surrey, Kent, Glamorgan, and Stafford slight disagreement.

*Reliability of these data.* There are three main reasons for thinking that these figures give fairly reliable conclusions. The most important is the close correspondence between the figures for the rural and urban districts for England and Wales, and frequently but less constantly between the towns and the surrounding country. This is shown in Tables I and II. A second reason is the relative constancy of the figures from year to year. Naturally the figures for any particular year may vary widely, but Table II shows that the difference between areas of high and low incidence is so great that in every single year the mortality rate is greater in Devon than in Essex. In Essex there was no year in which it was above 8 per million, but in Devon there was no year in which it was below 12, and only two in which it was below 17. Even when the county boroughs and the urban and rural districts of these two counties are given separately there are only three of the twenty-one different mortality rates for

Devon which are much below the higher figures for Essex, and only two of the twenty-one for Essex which are much above the lower figures for Devon. Hampshire is included as a county occupying an intermediate position.

TABLE II. *Deaths from Exophthalmic Goitre annually in Three Counties and Three County Boroughs.*

Area.	District.	Popula- tion.	Deaths from Exophthalmic Goitre per 1,000,000 living.							Aver- age.
			1913.	1914.	1915.	1916.	1917.	1918.	1919.	
Devon	Rural districts	227,000	26	13	13	5	22	31	13	17.6
Devon	Urban districts	221,000	32	36	23	18	5	5	36	22.0
Plymouth	County Borough	127,000	16	16	16	16	8	39	63	24.5
Devon	Total	575,000	26	23	17	12	12	23	33	21.0
Hampshire	Rural districts	237,000	8	12	17	17	8	12	17	13.0
Hampshire	Urban districts	214,000	14	14	14	5	10	5	14	10.8
Portsmouth	County borough	241,000	8	21	4	12	4	8	8	9.5
Hampshire	Total	692,000	11	16	11	11	7	9	13	11.1
Essex	Rural districts	265,000	8	15	19	4	8	4	8	9.0
Essex	Urban districts	777,000	8	6	5	5	1	3	9	5.3
West Ham	County borough	294,000	0	7	3	0	3	3	3	3.0
Essex	Total	1,336,000	6	8	7	4	3	3	7	5.5

The third reason for thinking that the period covered is long enough to give accurate results is that the counties with a high incidence do not appear to be jotted about on the map haphazard, but form natural groups. This will be seen most clearly when the map of distribution is studied.

There are two possible objections which must be considered: that death-rate does not give a good idea of the incidence rate, as the mortality may be very variable, and that deaths from exophthalmic goitre may be used to include rather different diseases of the thyroid in different places. Neither of these objections are easy to answer, but with a disease which is difficult to treat probably the mortality does not vary enormously in different parts of the country.

Of course the deaths which take place in hospital and after operation will often be shown in a wrong area, i. e. where they were not acquired. If hospital centres such as London, Birmingham, and Manchester showed a high death-rate it might be due to this, but actually they show a low death-rate; and in general the towns where the hospital patients die show a lower death-rate from exophthalmic goitre than the surrounding country areas where there are no hospitals. The great mobility of the population since the introduction of railways makes the same sort of difficulty.

The second objection really depends on the relative frequency of true exophthalmic goitre (Graves's disease) and hyperthyroidism following an adenoma of the thyroid. In an area where goitre is endemic, there are a large number of subjects with adenoma of the thyroid. Later in life some of these may develop

symptoms of hyperthyroidism, which may lead to a rather loose diagnosis of exophthalmic goitre. Perhaps for this reason the two forms of goitre are said to occur together round the Great Lakes of North America. It is difficult to know how far such cases might account for the deaths registered as from 'exophthalmic goitre', and this must be borne in mind in discussing the distribution of 'exophthalmic goitre', which is based mainly on the Registrar-Generals' figures.

To try and obtain further evidence about this the reports of the 111 patients admitted to Guy's Hospital with adenoma of the thyroid during the years 1920-23 have been examined. Although the great majority of these come from the surgical wards, where patients with symptoms of hyperthyroidism from adenoma of the thyroid would naturally be admitted, less than 15 per cent. have any such symptoms. Even if the reports are rather incomplete, the daily pulse-rate during their stay in hospital is always recorded, and this gives a reasonable diagnosis. There are other reasons for a rapid pulse and for nervousness, and actually the proportion with hyperthyroidism is less, so that during these four years there were probably about ten patients with hyperthyroidism following an adenoma.

During the same period there were over 60 patients with exophthalmic goitre, excluding those with milder symptoms who were diagnosed as hyperthyroidism. The only conclusion is that as far as the evidence from Guy's Hospital goes, serious symptoms arise much more frequently from exophthalmic goitre than from the so-called toxic adenoma. In a series of cases described by Berry (39) the proportion with symptoms of hyperthyroidism is also very low. Dr. Means tells me this is so at the Johns Hopkins Hospital, though it is not so in the north of the United States round the Great Lakes. It seems probable, though not proved, that the majority of deaths recorded as from exophthalmic goitre in the Registrar-Generals' reports are from true exophthalmic goitre, and that a much smaller proportion are from hyperthyroidism following an adenoma of the thyroid.

*Annual incidence.* The seven years 1913-19 are covered by the statistics of each area. In 1914 and in 1919 the figures were higher than in other years, being 16 per cent. above the average in 1919. As the time of onset of the disease is unknown, and nearly all the figures are affected by the war period, it is difficult to know if this is to be associated with the extra stress of the war.

In any case, if the 1913 figures can be taken as a standard for peace time, there was no great increase in deaths from exophthalmic goitre, in spite of its increased frequency among men during the war. The total number of deaths annually from 1913 to 1919 for Great Britain and Ireland were 492, 564, 527, 537, 497, 502, and 615.

*Age and sex incidence.* Unfortunately, these were not tabulated for England, but in Scotland one man died for every ten women, and in Ireland one man for every seven women. The age at death for the Scotch cases is given in Table III. It is very different for the age of onset, which is given for comparison from the Guy's Hospital figures (7). 80 per cent. of the cases there started between 15



and 34, while less than 30 per cent. of the deaths took place between 15 and 34, and 50 per cent. between 35 and 55.

TABLE III. *Showing Age at Death from 'Exophthalmic Goitre' (Scotland), at Onset of Exophthalmic Goitre (Guy's Hospital Cases), and on Admission to Hospital for Symptoms arising from Cystadenoma of the Thyroid.*

Age.	Age on Admission to Hospital for Symptoms of Cystadenoma (percentages).*	Percentage of Deaths from Exophthalmic Goitre at Various Ages.	Age at Onset of Exophthalmic Goitre (percentage).
Under 14	2	1	1
15-24	19	11	42
25-34	21	17	30
35-44	27	25	19
45-54	20	25	7
55-64	9	14	1
65 and over	2	7	—
Total number of cases	111	573	178

\* The age incidence given by Berry (39) of 500 patients who were operated on by him for various thyroid disorders, mostly adenomatous, is very similar to this.

*Distribution of exophthalmic goitre.* This is best shown by two maps. In the first (Fig. 1) large areas with a population of at least 2,000,000 are shown. In this way errors due to the smallness of the figures (from the counties being too small, or the period of observation being too short) are eliminated, and a general idea of the distribution of exophthalmic goitre is obtained. These large areas are obtained by combining one county with the neighbouring one with the most similar incidence, and so on, until areas of sufficiently large population are obtained.

There are 11 such areas, as the county boroughs of England are excluded. Scotland includes two where there are 11 deaths annually per million of the population living. The seven southern counties of Scotland have more deaths from Graves's disease, and are therefore combined with the four northern counties of England and part of Yorkshire where the index figure is 15.<sup>3</sup> An adjacent area made up of the rest of Yorkshire and the east coast counties as far south as Suffolk has the same figure.

On the west there are two areas with an even higher incidence, Lancashire, Cheshire, and Shropshire, with an index of over 17; and an area of nearly 4,000,000 comprising the whole of Wales, Devon, and the three south-western counties, with Gloucester and Oxford connecting these two areas. Here the index figure is over 16. On the east coast (north of and including part of London) is the area with the lowest mortality from Graves's disease. It includes Essex, Middlesex, and Hertford, and the index figure is only 8. The remaining counties form two areas, a midland and a southern group, with an intermediate incidence the same as in Scotland.

Ireland is made up of two areas, a narrow eastern strip where there are 10 deaths annually per million of population living, a little less than Scotland and

<sup>3</sup> The incidence of exophthalmic goitre is expressed as so many deaths annually per million of the population living. For convenience this is sometimes called the index figure.



the English midlands; and a broader western strip very sparsely populated with an index of only 3. Clearly the rarity of Graves's disease cannot be due to the sparse population, for central Wales has as much as anywhere. The figure for the west of Ireland is so much lower than elsewhere, that it is probably due to inaccurate statistics caused by the very disturbed condition of the country.

The disadvantage of this map is that sometimes areas in which the rarity of Graves's disease seems to be accurately given by the low index figure have to be combined with areas with a much higher incidence, e.g. Monmouth and Glamorgan are combined with the rest of Wales.

In the second map (Fig. 2) the result is given separately for each county. Except that in the comparatively few cases where the population of the county (in England without the county boroughs) is less than 100,000, it is combined with the adjacent county where the incidence is most similar. This map probably gives a more accurate idea of the distribution of exophthalmic goitre, because areas of much and little Graves's disease have not been combined; but occasionally the areas dealt with may not be large enough to give correct results.

But the counties are only administrative units and often combine areas of very different physical conditions, in one of which the incidence may be high and in another low. This map will now be described in greater detail. It is useful to remember that in Great Britain and Ireland as a whole there are 12.4, and in Great Britain alone 13.4, deaths annually per million living. The figures given in brackets after each county give the deaths annually for the same population.

#### *The South of England.*

There are three areas requiring special notice. In the south-west, Cornwall (25), Devon (22), and Somerset (22), have a large amount of Graves's disease, nearly twice as much as the rest of England. Adjacent to these is Dorset (9), with very little, but possibly the area is not large enough to give a reliable result. In the south-east, Kent (13), and still more Sussex (16), are above the adjacent counties in their incidence of Graves's disease.

#### *The North of England.*

With one exception (Durham (9)) there is more exophthalmic goitre than on the average. It is interesting that Durham is, like Monmouth and Glamorgan, an area with little Graves's disease surrounded by an area where it is much more common. Westmorland (27) seems to be the centre where there is most with decreasing incidence round it. In Lancashire (18), Cumberland (21), and the North (20) and East Ridings of Yorkshire (23) it is high. In Northumberland (14) and the West Riding of Yorkshire (15) and Nottingham (14) it is lower, but still above the average for England.

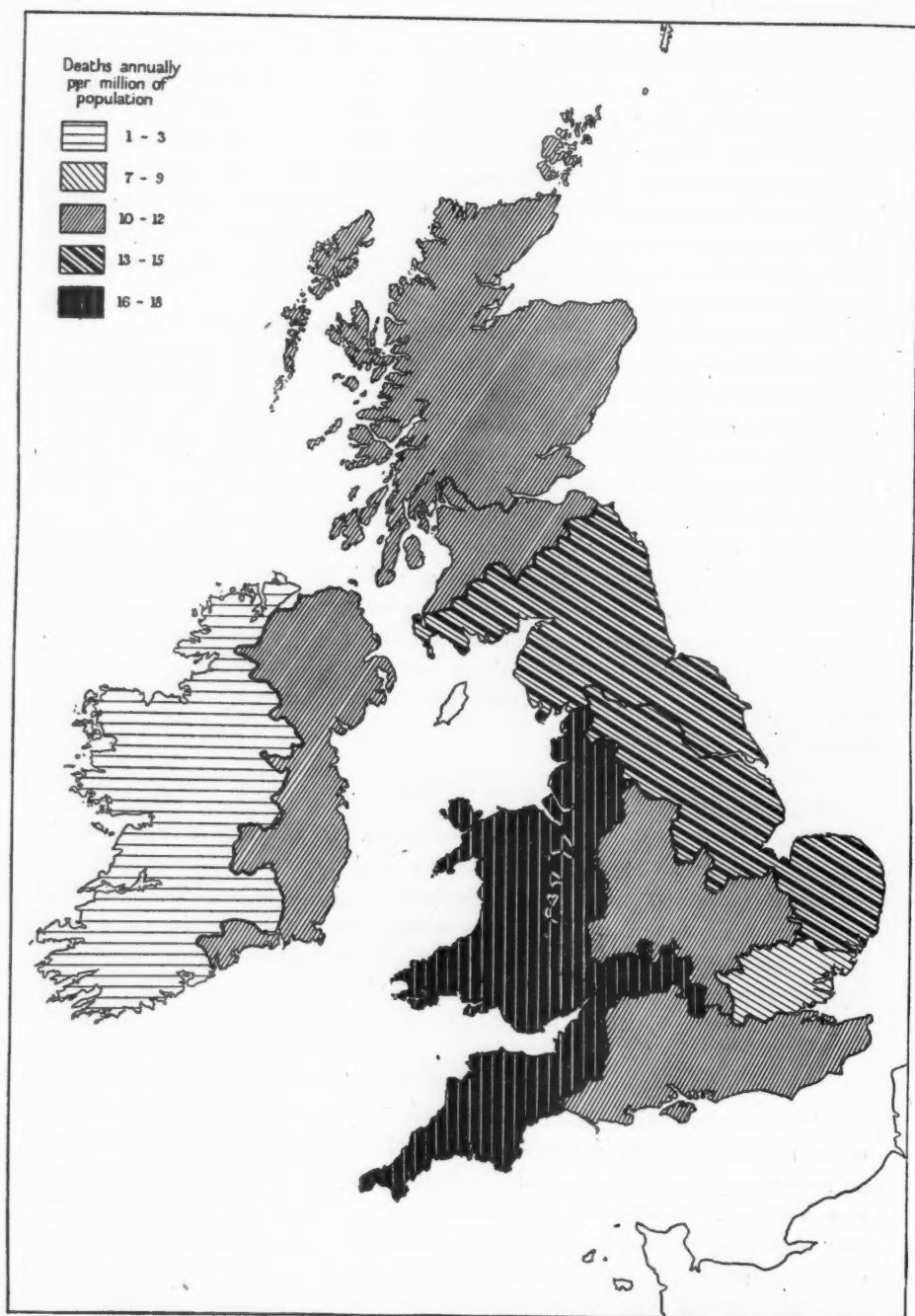


FIG. 1. Map of Great Britain and Ireland divided into eleven areas, which have each a population of 2,000,000 or more, to show the distribution of deaths from 'exophthalmic goitre' according to the Registrar-Generals' Reports.

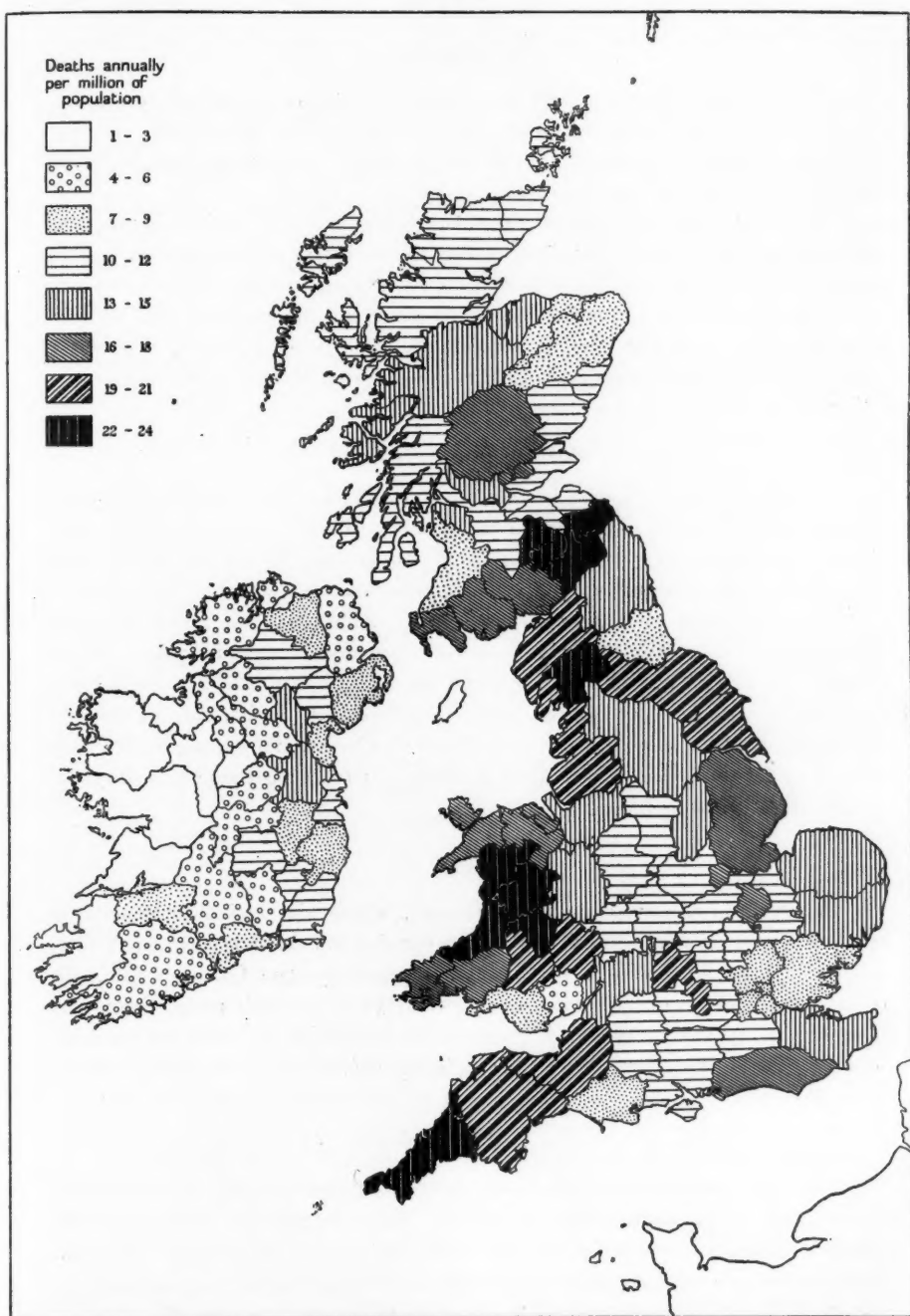


FIG. 2. Map of Great Britain and Ireland by counties, to show the distribution of deaths from 'exophthalmic goitre' according to the Registrar-Generals' Reports.

*The Midlands.*

The midland counties show an extremely uniform incidence of exophthalmic goitre, the index figure for each being between 10 and 12. Several southern counties, Hampshire, Wiltshire, Berkshire, and Surrey, can really be included with this group.

The one exception is Oxfordshire (24), where the incidence is twice as high as in any of the others. It might be that the numbers are not large enough to give reliable results, but the incidence is equally high in the city and in the urban and rural districts. Evidence from other sources confirms this, so that Oxford should really be considered with the west, being joined by Gloucester (the Cotswolds) to the other areas of high incidence in Wales and in Somerset.

*The East Coast of England.*

Generally the incidence is above the average. Kent has already been mentioned. The incidence is much the same in Norfolk (14) and Suffolk (15), higher in Lincoln (17), and still higher in Yorkshire. In the North (20) and East Riding (23) of this county it is about as high as in Devon and Cornwall.

The exception is the group formed by Middlesex (8), Essex (7), and Hertford (8), where the incidence is lower than anywhere in England. These figures are about the same as the figure for London, but they are not merely due to the urban areas of London included in Essex for administration; because the rural districts have equally little Graves's disease, and boroughs like East and West Ham have much less than a similarly situated borough like Croydon, on the Surrey side of London.

*Wales.*

Apart from Glamorgan and Monmouth, where the incidence of exophthalmic goitre is very low (9 and 5 respectively), it is high throughout Wales, but is highest in the centre—in Radnor, Montgomery, and Cardigan (33). In eight other Welsh counties it is more than twice as high as in Essex and London. A glance at the map gives an impression of a centre for Graves's disease in mid Wales, the incidence gradually decreasing as the distance from this increases.

*The West of England.*

The large amount of exophthalmic goitre in Somerset, Devon, and Cornwall has already been mentioned. Along the Welsh border, in Gloucester (13), Hereford (23), Shropshire (14), and Cheshire (15), the incidence is just above the neighbouring midland counties, but except in Hereford it is not as high as in most of Wales. In Lancashire (19), in spite of the change from the sparsely populated mountainous districts to one of the largest industrial areas of the world, the incidence is as high as in most parts of Wales.

*Scotland.*

The seven southern counties of Scotland form an area joining the northern group of England, and the incidence is equally high. In five of these, Berwick, Peebles, Roxburgh, Wigton, and Selkirk, the incidence is 32 deaths annually per million of the population—about the same as in central Wales.

Curiously enough in each there is one county, Selkirk in Scotland and Radnor in Wales, where the index figure is over 50. No other areas show figures nearly as high as this. Perhaps over a larger period of years there might not be quite so many cases, but it is noteworthy that each is the centre of an area of much exophthalmic goitre. Westmorland and Cornwall are similar centres in England, but the incidence is not so high. In Ireland there is no corresponding centre.

The only other places in Scotland worthy of special comment are the central Highlands with relatively high incidence—Inverness (14), Moray (19), Perth (19), and Stirling (15), and the eastern Highlands, comprising Aberdeen (7) and Banff (7), and the town of Aberdeen (7), with low incidence.

The other point of interest about Scotland is that it lends no support to two generalizations which can be made for the English figures. In England Graves's disease is more common round the sea-coast than inland, and more common in the country than in the towns. In Scotland it is if anything less common round the sea-coast than inland, and in the seven largest Scotch towns the incidence is not much lower than in the rest of Scotland (10.5 against 12.9). With the exception of Paisley, where there is a lot of exophthalmic goitre, the Scotch towns are generally the same as the surrounding country. The average figure for Scotland is practically the same as for England and Wales.

*Ireland.*

Few if any conclusions can be drawn about Graves's disease in Ireland, as over large areas the figures are so low as to make their accuracy doubtful. Probably the registration of the cause of death was very inadequate, owing to the disturbed state of the country during the period under review. Ireland appears to be divided into two areas—an eastern strip where the incidence is a little lower than in the English midlands, and a broader strip in the west where there are only just over 3 deaths annually per million of population.

This area can be subdivided into seven counties in the extreme west, where the index figure varies from 1 to 3, and an intermediate group of nine counties where the index figure is 4 or 5. These are the extremely low figures which make the Irish results very doubtful, but there is one small area of large population in England, e.g. Monmouth, with almost as little Graves's disease. In the east only one county, Monaghan, and Dublin city have as much exophthalmic goitre as the average for all England.



*The Towns of England and Wales.*

Separate returns are available for eighty county boroughs. Except for Canterbury, Chester, and Burton-on-Trent, the population of each is more than 50,000, and all the larger towns are included. It is tedious to consider all these in detail, but to show that there is a general agreement between the towns and the surrounding county the twenty with the highest and the twenty with the lowest death-rate from exophthalmic goitre will be discussed. (Many of the figures for these are given later in Tables VII and VIII.)

The former includes seven towns of Lancashire, viz. Rochdale, Blackpool, Bolton, Southport, Burnley, Blackburn, and Preston; three in Cheshire, Stockport, Wallasey, and Chester, the two former being practically on the Lancashire border; Carlisle in Cumberland; and three in the West Riding of Yorkshire, York, Huddersfield, and Dewsbury, with a water-supply from the Pennine chain between Lancashire and Yorkshire (36).

Of the remaining six, Oxford and Plymouth occur in counties with a very high incidence, and Hastings and Eastbourne in Sussex with a rather high incidence. The only two towns which seem to be exceptions are Bournemouth and Burton-on-Trent, which themselves gave a high incidence and occur in counties with less than the average amount.

London is just excluded from the other twenty towns with little exophthalmic goitre, but the two with the least, East and West Ham, are in Essex. Three, Sunderland, South Shields, and Gateshead, are in Durham, the only other English area with as little as Essex.

Four are in midland counties where the amount of Graves's disease is below the average, Smethwick, Walsall, West Bromwich, and Northampton. Southampton is also in an area of low incidence, so that half the towns of this group are in good agreement with the surrounding country.

With the other half there is a much less close agreement. Norwich and Lincoln in the east, Barrow-in-Furness in Cumberland, Leeds, Rotherham, Hull, and Halifax, in Yorkshire, and Wigan, St. Helen's, and Salford, in Lancashire, occur in areas with an high incidence. Some discrepancies would be expected from the smallness of the figures, but not to such an extent as this. Another factor associated with the incidence of exophthalmic goitre will be discussed later, and as the towns of Lancashire and Yorkshire provide the main exceptions they will be referred to in greater detail.

*General distribution.* To what general causes can this geographical distribution of exophthalmic goitre be attributed? Its incidence in England and Wales suggests three main conclusions. Graves's disease is more common in the mountains of the west and north than in the plains of the midlands and the south. It is more common round the sea-coast than inland. It is more common in the rural than the urban districts, and more common in these than in the towns.

The last is only partly true, because large industrial towns in an area with



much Graves's disease show a much higher incidence than rural districts in an area with little Graves's disease. And it only seems to be true in England and Wales. In Scotland the towns generally agree with the surrounding country. The same is true in Ireland for Dublin and Belfast, for which there are separate figures.

It is the locality which is of much greater importance than the question of town or country. The big industrial areas of Birmingham and the surrounding towns and of Glasgow have an incidence similar to that for the country round them, and the towns of Lancashire, one of the biggest industrial areas of the world, have more Graves's disease than the English country districts. In a group of nine large towns in the north and east of Lancashire there are over twenty deaths annually per million of population, more than twice as many as in London.

But the three areas with the least Graves's disease in England are industrial and densely populated, e.g. Middlesex with parts of Essex and Hertford, Glamorgan and Monmouth, and Durham. Two of these are actually centres of the coal-mining and coal-exporting industries.

Two processes seem to be at work in a large town or industrial area; one has the same influence on the town as in the surrounding country in tending to produce Graves's disease, and the other tends to make it less than in the surrounding country. In different parts either influence may be the stronger. A few towns show an incidence quite different to the surrounding country. This may be due to a water-supply from a distant area and will be discussed later.

The English figures suggest two other generalizations on the effect of mountains and of the sea in increasing the amount of Graves's disease. In England and Wales the effect of the sea is striking, though it is true all the four areas of low incidence are also on the sea-coast. In Ireland proximity to the sea seems to be without effect, and in Scotland the incidence of Graves's disease seems to be greater inland.

The influence of mountains seems to be the most important single factor, and the map of England and Wales marking mountain ranges gives somewhat the same effect as the map showing the distribution of exophthalmic goitre. But against this must be set the comparatively low incidence of the mountainous areas of Scotland. Nor do the Irish figures lend much support to the view that exophthalmic goitre occurs especially in mountainous regions.

One other point suggested itself as a possible factor. Wales and Cornwall with their high incidence of exophthalmic goitre are mostly the old Celtic population, and their excitable temperament might well make them more liable to develop the disease. But this is not found among the women of the dales and industrial areas of Lancashire or with the lowland Scot.

So far all the factors discussed have seemed true for some parts, but not universally true. The geological map of England seems to have a still closer connexion with the incidence of Graves's disease. In view of the importance of iodine in the physiology of the thyroid, the clue may be found in the effect

of the geological formation and the iodine content of the water. These factors will be discussed subsequently, after the distribution of endemic goitre has been more fully established.

*Part II. Distribution of Endemic Goitre in England.*

In spite of the accurate knowledge about the distribution of goitre in most parts of the Continent, there is little definitely known about it in England. Osler states that it is common in Derby, Sussex, and Hampshire, and very prevalent in Oxford and the upper Thames Valley (8).

Hirsch has no actual figures for England, but has collected references to a great many papers describing the occurrence of goitre (9). His summary is as follows: In the south one of the larger centres is found among the chalk hills of Sussex (in and around Horsham) and Hampshire, and in the more elevated parts of Surrey, particularly Haslemere.

In the west goitre is endemic at several places in Monmouth, in the Forest of Dean (Gloucester), at Worcester, Stourport, and other places in Worcestershire, in one district of Cheshire, and in many parts of Wales. In the eastern counties there is a considerable centre of goitre in Norfolk. It is endemic at Ridgemont in Bedford and near Beaconsfield in Buckingham.

In the midlands it is endemic in Warwick, in the coal districts of Nottingham, above all in Derby, and in the hilly parts of Stafford. Lastly, from the northern counties we have information of endemics of goitre at Bolton, Padiham, Church, and Accrington in Lancashire, in Yorkshire, in some parts of Durham and Westmorland, in the lead mining district of Cumberland, and in the west of Northumberland.

In Scotland goitre is much less frequent than in England. The interior of Perth and the east coast of Fife are given as its chief seats; there are also centres in the southern counties in the east of Wigtown, in Kirkcudbright, in Dumfries and Roxburgh, in the west of Berwick, in Selkirk, Peebles, and Lanark; and in Ayr and the island of Arran. The north of Scotland appears to be free from it. From Ireland there is no special information about goitre, but the disease occurs endemically in a few localities. His conclusion is that the amount of goitre in England is comparatively large, and there is more of it in the south and midlands than in the northern and mountainous districts. This conclusion does not follow at all obviously from the distribution of goitre just quoted. In Scotland the areas of endemic goitre seem to be just the places where exophthalmic goitre is frequent (see p. 201). As regards England and Wales it is more difficult to decide, but the four centres mentioned in Lancashire are at the edge of the hills close to towns where the death-rate from exophthalmic goitre is especially high.

McCarrison discusses the distribution in many parts of the world, but only makes the following references to Great Britain: 'It is so common in certain parts of England and Scotland as to be distinguished by the names Derbyshire

neck and Nithsdale (Dumfries) neck. It is not always common in mountainous areas; for example, certain parts of Norway and the Highlands of Scotland are almost exempt' (10). Elsewhere (12) he is quoted as saying that it is common in the dales of Lancashire and Yorkshire as well as Derbyshire.

Much the fullest description is given by Berry (11). Those interested should consult his account, as it can only be given briefly here, and it is difficult to be sure that it has been summarized fairly.

Endemic goitre occurs very sparingly in most of Surrey and Essex—sparingly over the villages on the Bagshot sands between Aldershot and Chertsey—hardly at all round Loughton, Chigwell, Harwich, Colchester, or Chelmsford. It occurs slightly but fairly uniformly in Hertford (Hatfield, Hitchin, and Hadham), and in the north of Essex and Suffolk, especially in the valley of the Stour. Parts of Norfolk are also affected. In Bedford there is a small amount throughout the county and a large amount in the south round Ampthill and Woburn.

In Hampshire it is not common and it occurs sparingly over the chalk of the North and South Downs. But in other parts of Sussex and Kent, especially in the more hilly parts of the Wealden area, it is common, e.g. at Cuckfield, Horsham, and Hadlow.

It is frequent at the junction of the oolite and liassic formations, i.e. in a narrow area passing through the counties of Gloucester, Oxford, Buckingham, Northampton, and Lincoln. To the west of this it occurs in many parts of Somerset, at Chiselborough, at Clevedon, and in the Mendips. In Gloucester it is fairly frequent, being common in the Forest of Dean at Wootton-under-Edge, Stroud, and Northleach, and in the villages east of Cheltenham. It is common in the south of Northampton and in Warwick at Chacombe, Warrington, Avon Dassett, and especially at Napton. It occurs in many of the villages east and south-east of Leamington, but very sparingly to the west.

It is almost absent in the south of Derby and rare in Nottingham. There is a very large amount in the carboniferous limestone in the east of Derby, at Cromford, Matlock, Youlgrave, Bakewell, Baslow, Stony Middleton, and Ashbourne. It is also common in similar areas in the east of Stafford. In Yorkshire it occurs round Knaresborough and Helmsley, but does not seem to occur at Ilkley. In Northumberland it is not common.

Goitre does not occur at Ilfracombe, and this is probably true for the north of Devon and for the west of Somerset. The parts of Dartmoor round Widdicombe are free from goitre. In Wales there is little information, but it occurs at Llanelly and on the shores of the Burry estuary in Glamorgan, and is said not to occur in Anglesea and in Brecknock. Probably it does not occur frequently in most of Wales.

The above contains much valuable information about the local distribution of goitre, which is difficult to summarize. Berry's own conclusions are geological rather than geographical. Endemic goitre occurs mainly on the calcareous rocks which are widely distributed in England—on the calcareous sandstones as well as on the limestones. It is doubtful if it ever occurs as an endemic disease on

the non-calcareous rocks. The igneous, metamorphic, Cambrian, Silurian, Devonian, Yoredale, and millstone grit rocks, and some of the non-calcareous parts of the coal measures and tertiaries appear to be mainly free from it.

Some part of this conclusion seems to be extremely doubtful, as there is evidence from other sources of large amounts of goitre in Devon, most of Wales, and in Lancashire.

After considering these accounts, it is still difficult to be sure of the distribution of endemic goitre in England. Obviously, without statistics it will be impossible to reach definite conclusions, and there are few actual figures for the British Isles.

*Results of school medical inspections.* The only statistical evidence is from the reports of various school medical officers. Their interest may be in quite different aspects of the question, and their reports may be presented in such different form and with such different ideas about the meaning of goitre that comparison is difficult.

Since 1919 there are seven reports on this subject in county areas for Cheshire (12), Worcester (18), Devon (19), South Kent (22), Shropshire (25), Durham (29), and East Suffolk (30). It is more likely to arouse interest in areas where there is endemic goitre, and in five of these there is a large amount, nearly 10 per cent. among all the children attending school, and 20-40 per cent. among the girls in their last year. Probably this high percentage includes some very slight cases of enlargement of the thyroid. In addition it is said to be frequent in reports from Derbyshire and Merioneth.

Among the towns, only Smethwick (16), Glossop (26), and Swindon (24) show at all a comparable incidence of goitre, and the latter is the centre of a large agricultural area. In Bath (13), Derby (14), Northampton (14), Leicester (15), Cardiff (17), Warrington (20), and Bolton (28) the incidence is between  $\frac{1}{2}$  and 2 per cent. of all the school children inspected. As in the other districts there is a higher percentage among the girls leaving school, varying from 2 to 7 per cent. The results of these various reports are summarized in Table IV.

An epidemic of goitre affecting eight boys has recently been described in some cottage homes at Rochdale in Lancashire (32). As is well known, these epidemics nearly always occur among soldiers in barracks or children at schools, and always in areas where goitre is endemic. So this may be taken as further evidence of endemic goitre in certain parts of Lancashire.

One or two additional facts may be mentioned. As Montgomery was one of the areas with a high death-rate from exophthalmic goitre, I wrote to a friend in practice there. Dr. Cockshut replied: 'This district (round Llanidloes) is full of endemic goitre. It is rich in minerals of the lead group and there is more goitre round the old mines. The usual type is a parenchymatous enlargement, appearing about puberty and amenable to treatment with iodine or thyroid extract. Symptoms of hyperthyroidism are rare.'

There are several other points of interest touched on in these reports. The very high incidence at schools in some districts is referred to in Bath, Leicester,

# GEOGRAPHICAL DISTRIBUTION OF EXOPHTHALMIC GOITRE 207

Kent, Shropshire, and Worcester. In the latter it is especially in the Rock and Tenbury districts, in sheltered villages bordered by high hills. In Shropshire it is specially in the south, and in Kent it is common in the triangle formed by Maidstone on the north and Edenbridge and Sandhurst on the south, and most of all round Cranbrook. In Kent the rural districts are affected much more than the urban, as is also the case with exophthalmic goitre. In Leicester it is more frequent in the wealthier parts of the town, and this too seems to be true in the relative distribution of exophthalmic goitre in London. The hereditary nature of the condition is referred to frequently (12, 17, 19, 22).

TABLE IV. *Incidence of Goitre in Boys and Girls of all School Ages, and in Boys and Girls during their Last Year at School, as given by Various School Medical Inspections during the Last Few Years.*

Town or County.	Year.	Number of Children seen (all Ages).	Percentage with Goitre (all Ages).		Number of Children (12-14).	Percentage with Goitre (12-14).	
			Boys.	Girls.		Boys.	Girls.
Cheshire	1919	2,000	6.0	16.4	700	12.0	38.0
Worcestershire	1921	1,200	7.0	17.0	—	11.7	29.0
Devon	1921	18,200	4.2	10.2	—	—	—
South Kent							
{ endemic areas }	1922	—	—	—	{	16.0	36.0
{ other areas }						2.7	21.0
Shropshire	1923	9,200	1.8	3.5	3,100	3.7	7.1
Durham (Upper Weardale)	1923	500	10.5	22.1	150	18.4	34.9
East Suffolk	1923	5,900	1.6	5.8	1,300	2.0	14.2
Derby	1916-18	—	—	1.9	—	—	—
Northampton	1918	—	—	0.5	—	—	—
Bath	1919	7,000	0.5	1.5	2,300	1.0	2.2
Leicester	1919	11,000	—	1.8	5,300	1.1	5.8
Leicester	1920	13,500	1.0	3.6	4,200	2.0	7.6
Smethwick	1920	3,500	3.8	9.0	—	—	—
Cardiff	1920	12,000	0.4	0.8	—	—	—
Warrington	1921	14,200	0.3	2.0	2,800	0.5	5.3
S.E. London	1922	1,800	3.8	4.6	—	—	—
Swindon	1923	2,300	5.2	12.0	900	8.5	22.8
Glossop	1923	1,900	—	4.8	—	—	—
Acton	1923	—	—	—	1,000	0.0	6.2
Bolton	1923	7,100	0.5	1.4	2,500	0.8	3.1

In general, the goitre is the endemic type with symptoms of hypothyroidism. The mental backwardness of these children is specially commented on in Cheshire, and the physical backwardness and small size in Derbyshire. The improvement after treatment with iodine is mentioned in Cardiff and Smethwick. In all these cases the goitre is due to decreased function of the thyroid tissue, the enlargement being a secondary attempt to compensate for this deficiency, in response to physiological needs. But this does not seem to be so everywhere. In Devon 14 per cent. of the goitres are associated with symptoms of hyperthyroidism, and only 2 per cent. with at all severe symptoms of hypothyroidism (19); and in Kent the girls affected are frequently well grown and well developed, with



a tendency to early menstruation and to functional disorders of the heart (22). Brewer at Swindon and Boul in East Suffolk find the same thing, the girls having often a tremor and rapid pulse (23). Brewer states that they improve with tincture of iodine painted over the thyroid or in the axilla, or with colossal iodine by mouth, but not with iodide of potassium by mouth—conclusions which require further investigation.

Eady finds that of 100 goitrous mothers there were born 361 girls and only 204 boys (18). The material is not very extensive, but there is a big difference in the numbers. The point is worth further attention in view of the experimental conditions under which the ratio of female to male births may be greatly increased (34).

All the reports agree that goitre is much commoner in girls than in boys at all ages, and that in both its incidence increases during school life, especially in girls at puberty. Full figures for the age incidence are given in three reports (12, 13, 20).

The facts are not really sufficient to state dogmatically the incidence of endemic goitre for the British Isles, especially as more evidence is hoped for in the near future.

During the present year (1924) the Board of Education has arranged that at the routine examination of all the children leaving school a special inquiry shall be made about the incidence of goitre. From the reports already discussed few general conclusions have been drawn, because it is very difficult to be sure that the same standard of enlargement of the thyroid has been used. An attempt to avoid this difficulty has been made by asking the medical officers to use a very simple classification, dividing the children into 'those in whom the thyroid is sufficiently enlarged for the increase in the size of the neck to be noticed on casual inspection (without measurement or palpation) and those in whom it is not so enlarged'. In this way it is hoped that a real idea of the distribution of endemic goitre throughout the country will be obtained.

Some of the most definite evidence about a local endemic of goitre is contained in the report of M'Gonigle from Durham (29). He found that in Upper Weardale there was a much larger proportion of children with goitre than in other parts of the county, and that, following the River Wear from its source, goitre was common to just below Wolsingham, but was rarely found from there down to the mouth of the river at Sunderland. This report illustrates another difficulty. If the figures for Upper Weardale were combined with those for the administrative county of Durham they might lead to few or even to wrong conclusions. A real map can only be prepared by combining together the reports of a large number of men with local knowledge, as it is now hoped to be able to do so.

In spite of the almost complete survey of the male population for recruiting the only facts available are that in 1917-18 in various towns in the west midlands about 8 men in 1,000 were rejected for various forms of goitre. The towns included were Birmingham, Burslem, Worcester, Coventry, Shrewsbury, Hereford,



Leamington, Walsall, and Wolverhampton. In Shrewsbury there was more, and in Burslem and Hereford less than the average (31). The total figures for Liverpool were very similar, and also for Edinburgh, but in Liverpool there were about an equal number of rejections for goitre and Graves's disease, while in Edinburgh all the cases were endemic goitre and nearly all came from small areas on the slopes of two hills (31).

*The prevention of goitre.* The question of endemic areas of goitre has become of special importance since it was shown that the disease could be prevented by the administration of iodine. This has been used for centuries in the treatment of goitre almost unknowingly, and its use was urged specifically by Coindet nearly a hundred years ago (33). But it has been brought into prominence recently by the good results obtained by Kimball and Marine (37) in the schools of Ohio. Some of the results they obtained are shown in Table V.

TABLE V. *Showing the Result on the Enlargement of the Thyroid of the Administration of Iodine.*

Condition of the Thyroid at First Examination.	Condition of the Thyroid at Subsequent Examination.				
		With Treatment.		Without Treatment.	
		Number.	Per-centage	Number.	Per-centage.
Children with no enlarge- ment of the thyroid	{ Remained normal	469	100	496	84
	{ Increased	0	0	94	16
Children with a small goitre	{ Decreased	218	38	170	28
	{ Unchanged	354	62	424	69
	{ Increased	0	0	17	3
Children with a large goitre	{ Decreased	51	64	30	37
	{ Unchanged	29	36	52	63

The steps which might be taken to bring about equally satisfactory results have been discussed by the school medical officers for Glossop (26) and Durham (29). In view of the mental and physical backwardness of many children with goitre, this is a question of the greatest practical importance from the point of view of the public health.

#### *Summary of Distribution of Endemic Goitre.*

Endemic goitre seems to be more common than the average in certain parts of Sussex, Kent, and Hampshire; in a strip along the north of the Chilterns, including parts of Buckingham and especially the south of Bedford; in parts of Norfolk; farther west in Oxford, and the Cotswold area of Gloucester and Warwick; and in the extreme west in Somerset and Devon (Cornwall not known).

In parts of Wales it seems to be very common, and it certainly occurs in Glamorgan. In the north it occurs in large amounts in the east of Derby and part of Stafford; in the Pennine chain affecting many parts of Lancashire and some parts of west Yorkshire, and farther north on both sides of the Border. In

Scotland it occurs in the six southern counties and especially in Dumfries, Essex and the Scotch Highlands seem to be the only places where all are agreed that it is comparatively rare.

*Relationship of Endemic and Exophthalmic Goitre.*

If this is an accurate summary of the distribution of endemic goitre, and if the deaths returned as 'exophthalmic goitre' are true Graves's disease, it follows that in the British Isles exophthalmic goitre is more likely to occur in connexion with areas of endemic goitre. An opposite opinion was held at first (7), largely because Derbyshire did not show a specially high death-rate from exophthalmic goitre. If this view is correct, it is contrary to McCarrison's experience in the Himalayas, to Bircher's in Switzerland, and to Berry's in England. It is the view which is generally expressed about the northern parts of the United States, though it is possible that this is only because there is there more hyperthyroidism after adenoma of the thyroid than true Graves's disease.

In the hopes of obtaining further evidence, the residence of the patients who were admitted to Guy's Hospital for all disorders of the thyroid during the four years 1920-3 was recorded. There were 111 patients with cystadenoma of the thyroid and 29 with parenchymatous goitre. Probably the former occurs most frequently in areas where goitre is endemic, so these two may be taken together, making 140 cases. There were 62 cases of exophthalmic goitre and 11 cases with less marked symptoms who were diagnosed as hyperthyroidism, making 73 in all during the same period. From a previous series of cases of exophthalmic goitre in the hospital between 1908-17 there were 85 where the address was available, so that 158 cases of exophthalmic goitre could be compared with 140 of parenchymatous enlargement and cystadenoma of the thyroid.

Often of course the residence actually given is not where the patient has lived most of her life, but sometimes there was a note of this and the real residence could be obtained. The results were strikingly different. Many more patients with exophthalmic goitre came from London and many more with cystadenoma of the thyroid came from the country. The results are shown in Table VI.

Of course the only figure which is any way significant is the proportion of cases of the two types of goitre coming from any particular area. Apart from the obvious difference between the proportion for London and the country, there is no significant difference between the counties where there are many or few deaths from exophthalmic goitre according to the Registrar-Generals' reports.

# GEOGRAPHICAL DISTRIBUTION OF EXOPHTHALMIC GOITRE 211

TABLE VI. *Showing the Residence of Patients admitted to Guy's Hospital with Disorders of the Thyroid.*

Locality.	Percentage Distribution of Exophthalmic Goitre.	Percentage Distribution of Cystadenoma of the Thyroid.
Bermondsey and Southwark	17	11
Rest of London	43	31
Kent and Surrey near London	20	13
Total London and near	80	55
Total outside London	20	45
Counties in which there are a relatively large number of deaths annually from exophthalmic goitre, e. g. Kent, Sussex, Norfolk, Suffolk, Lincoln, Lancashire, Yorkshire, Oxford, Gloucester, Somerset, and Devon	10.3	26
Counties in which there are relatively few deaths annually from exophthalmic goitre, e. g. Essex, Hertford, Bucks., Berks., Northants, Bedford, Cambridge, Surrey, Hampshire, and Wiltshire	9.7	19

## Part III. Exophthalmic Goitre and the Birth-rate.

It is well known that Graves's disease is most likely to occur in women who are not married or have not had children. But the number of women with exophthalmic goitre is relatively so small, that this could not influence the birth-rate of a district. It is therefore surprising to find that in most towns with a high death-rate from Graves's disease there is a low birth-rate and vice versa.

This can be shown in two ways, by finding a large amount of Graves's disease in the towns with the lowest birth-rate, or a low birth-rate in the towns with most Graves's disease. Both these are shown in Table VII. Only fifteen towns are given because five are included in the list of the ten towns with the lowest birth-rate, and also in the list of the ten towns with the highest death-rate from exophthalmic goitre. With the exception of Bournemouth and Burton-on-Trent, all the towns are in counties where there is a relatively large amount of Graves's disease. The birth-rates are for the year 1921, which was chosen at random. The other figures are for the years 1913-19, but it does not seem likely that this is a serious disadvantage. On the whole the ten towns with the most exophthalmic goitre have an average birth-rate of 16.9 against 23.9 per thousand in the ten towns with least.

From the other point of view the result is even more striking, for the ten towns with the lowest birth-rate have 19.6 deaths from exophthalmic goitre annually per million of population living, against 6.9 for the ten towns with the highest birth-rate.

The second group of figures for the towns where there is a high birth-rate

TABLE VII. *Showing the Relationship of a High Death-rate from Exophthalmic Goitre and a Low Birth-rate. The Ten Towns with the Lowest Birth-rate and the Ten Towns with the Highest Death-rate from Exophthalmic Goitre are all included.*

Town and County.		Death-rate from Exophthalmic Goitre.		Birth-rate. Town.	Order by Lowest Birth-rate.
		County.	Town.		
Hastings	Sussex	16.0	30.9	15.6	7
Rochdale	Lancs. (N.)	18.6	30.7	17.0	—
Blackpool	Lancs. (N.)	18.6	30.4	14.8	5
Wallasey	Cheshire	18.6	27.1	17.4	—
Bolton	Lancs. (N.)	18.6	24.8	18.6	—
Plymouth	Devon	21.7	24.7	19.6	—
Oxford	Oxford	24.0	23.7	15.9	8
Bournemouth	Hants	12.6	22.7	18.8	3
Burton-on-Trent	Stafford	12.3	21.3	22.5	—
Eastbourne	Sussex	16.0	21.1	13.7	2
Southport	Lancs. (N.)	18.6	20.0	14.0	4
Blackburn	Lancs. (N.)	18.6	17.0	16.7	10
Huddersfield	Yorks. (W. R.)	15.1	17.0	12.5	1
Bath	Somerset	22.3	10.1	15.4	6
Halifax	Yorks. (W. R.)	15.1	3.0	15.9	9
Average of the ten towns with the highest death-rate from exophthalmic goitre		17.7	25.8	16.9	
Average of the ten towns with the lowest birth-rate		17.7	19.6	15.1	

TABLE VIII. *Relationship of a High Birth-rate and a Low Death-rate from Exophthalmic Goitre. (Compare Table VII.)*

Town and County.		Death-rate from Exophthalmic Goitre.		Birth-rate. Town.	Order by Highest Birth-rate.
		County.	Town.		
West Ham	Essex	7.4	3.0	32.4	2
Halifax	Yorks. (W. R.)	15.1	3.0	15.9	—
Sunderland	Durham	8.6	3.7	28.6	8
East Ham	Essex	7.4	3.9	26.7	9
Rotherham	Yorks. (W. R.)	15.1	4.4	24.4	—
Walsall	Stafford	12.3	4.6	25.4	—
Southampton	Hants	12.6	4.7	20.3	—
South Shields	Durham	8.6	5.0	26.6	10
Smethwick	Stafford	12.3	5.7	21.4	—
Leeds	Yorks. (W. R.)	15.1	6.0	19.8	—
St. Helens	Lancs. (S.)	218.6	7.3	29.1	6
Gateshead	Durham	8.6	7.7	32.8	1
Stoke-on-Trent	Stafford	12.3	9.0	29.0	7
Liverpool	Lancs. (S.)	218.6	9.1	32.0	3
Merthyr Tydfil	Glamorgan	9.3	9.7	29.7	5
West Hartlepool	Durham	8.6	11.1	32.0	4
Average of the ten towns with the lowest death-rate from exophthalmic goitre		11.4	4.5	23.9	
Average of the ten towns with the highest birth-rate		13.4	6.9	29.9	

and relatively little exophthalmic goitre are shown in Table VIII. Again, many of the towns are in the counties which have little Graves's disease—Essex, Durham, and Glamorgan. Lancashire has been qualified as north or south because such a large county affords the opportunity for a complete change of the physical conditions. Among other differences the towns included as in the north are mainly in the foot-hills, and the towns of the south mainly in the plains.

At first sight there are two objections to drawing any conclusions from this association. The first is that the high death-rate from exophthalmic goitre is merely part of a general high death-rate, which might naturally be associated with a low birth-rate. As a large number of elderly people go to a town like Bournemouth, a relatively high death-rate and a low birth-rate might be expected.

It is easy to show that this has nothing to do with the different birth-rates in the two groups discussed, for if these towns are grouped by the death-rates the average general rate is practically the same in the towns with most and least deaths from exophthalmic goitre. If the two towns at the extreme of each group are omitted, the general death-rate varies between 12.1 and 14.8 per thousand for one group, and 10.9 and 14.6 for the other.

The second objection is a more valid one. It is that large industrial towns are being contrasted with smaller residential towns. For example, among the towns with a low birth-rate are Oxford, Bournemouth, Eastbourne, and Bath, which cannot fairly be compared with East and West Ham, Leeds, Southampton, and Merthyr Tydfil. The high birth-rate of the larger industrial towns, and especially of the mining districts, is well known. But there are several large industrial towns in the first group with a low birth-rate.

This difficulty can be best avoided by taking the industrial towns of a fairly uniform area. I have chosen Lancashire, Yorkshire, and Cheshire. All towns of less than 80,000 inhabitants have been excluded, Bootle and Salford have been combined with Liverpool and Manchester as they contain a selected population, and Southport, Blackpool, York, and Chester have been omitted as they are not industrial.

All other towns of these three counties have been included in Table IX, which shows that as the birth-rate decreases, exophthalmic goitre becomes more frequent. There is no regular increase and there are marked exceptions, but this is only to be expected if other factors such as the water-supply are also of importance in the production of Graves's disease. Halifax is the worst exception, and as its population is only 100,000 it is hardly significant. Oldham and Leeds with much larger populations are less extreme exceptions. It seems quite fair to compare these towns, from the general similarity of their social and industrial conditions.

The results for all the largest eighty towns are shown in Fig. 3. Naturally when so many factors are concerned the points cannot be expected to be exactly on a curve, but it is quite clear that there are no towns with a high death-rate from exophthalmic goitre and a high birth-rate, and a very few towns with a low

death-rate from exophthalmic goitre and a low birth-rate. 90 per cent. of the towns lie in the shaded area, and the average of all these towns is represented by the central broad line. As far as the towns of England are concerned there is some association between a high death-rate from exophthalmic goitre and a low birth-rate.

TABLE IX. *Death-rate from Graves's Disease and Birth-rate in Towns of Lancashire, Yorkshire, and Cheshire.*

No.	Town.	Death-rate from Graves's Disease (per 1,000,000).	Birth-rate (per 1,000).
1	St. Helens	7.2	29.1
2	Liverpool and Bootle	9.5	28.8
3	Middlesbrough	12.6	28.0
4	Birkenhead	15.0	25.8
5	Kingston-on-Hull	6.0	24.2
	Average 1-5	10.1	27.6
6	Wigan	7.9	22.4
7	Manchester and Salford	11.1	21.4
8	Sheffield	10.9	20.6
9	Preston	15.7	20.6
10	Bradford	13.3	20.5
	Average 6-10	11.8	21.1
11	Stockport	20.7	20.3
12	Leeds	6.0	19.8
13	Oldham	8.6	19.3
14	Burnley	19.6	18.6
15	Bolton	24.8	18.6
	Average 11-15	15.9	19.3
16	Walasey	27.1	17.4
17	Rochdale	30.7	17.0
18	Blackburn	17.0	16.7
19	Halifax	3.0	15.9
20	Huddersfield	17.1	12.5
	Average 16-20	19.0	15.9

The most likely explanation of this association is that something in the social conditions leads to a low birth-rate, and that this leads to a relatively large amount of exophthalmic goitre among the women who are unmarried and have no children. The employment of large numbers of women in factories before and after marriage suggests itself as the probable cause, and among the towns with the lowest birth-rate and a large amount of exophthalmic goitre are Huddersfield, Blackburn, Burnley, and especially Rochdale and Bolton.

But all these towns are also in an area where exophthalmic goitre is endemic, and it looks as though a large mortality most often occurs where both factors are unfavourable—the water-supply or some other physical factor, and a relatively large number of women employed in factories or unmarried. This may be for industrial reasons, as in Rochdale, Bolton, &c., or for social reasons, as in Bournemouth, Bath, Oxford, &c.



The other possible explanation is that the primary factor is the water-supply or the other physical conditions making exophthalmic goitre common, and that this leads directly to the low birth-rate, the social and industrial factors being unimportant. It cannot act simply by its influence on the women with Graves's disease, but must affect the female population as a whole, with a consequent low birth-rate. This seems unlikely, but so important that it is worth investigation.

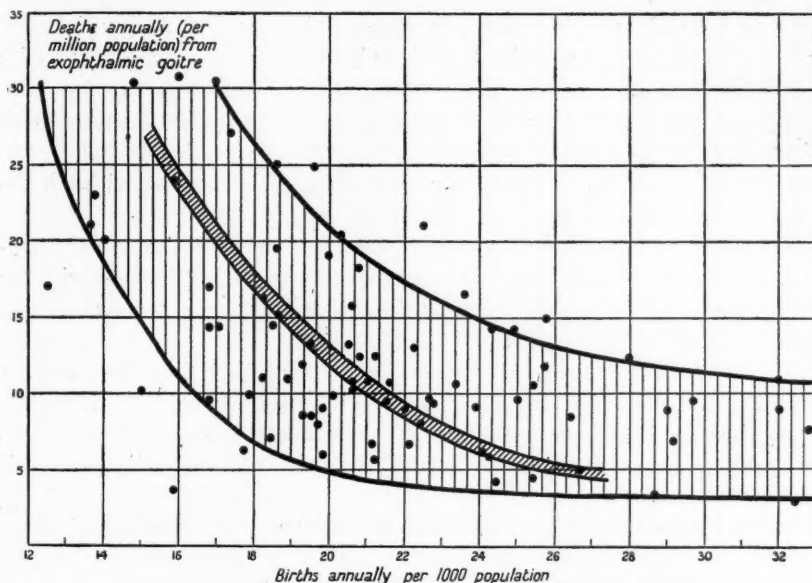


FIG. 3. Showing relationship of death-rate from Graves's disease and the birth-rate.

Can any other evidence be obtained that a low birth-rate is associated with a prevalence of exophthalmic goitre? There is a large difference between the amount of Graves's disease in various county areas. Is this associated with differences in the birth-rate? It must be acknowledged at once that there is no very close connexion, but there is some. In Wales, Radnor, Montgomery, and Cardigan have most exophthalmic goitre and the birth-rate is 18.8 per thousand, while in Glamorgan and Monmouth, where there is little exophthalmic goitre, it is 30.8.

In England, Durham has a birth-rate for the county much above the average (31.2) and has little Graves's disease, but Essex, Middlesex, and Hertford have an average birth-rate. After Durham, the highest birth-rates are in Stafford, Northumberland, Nottingham, Derby, and the West Riding of Yorkshire, which all include large industrial areas.

At the other extreme Sussex has the lowest English birth-rate (16.1), and its incidence of exophthalmic goitre is much the same as the counties just mentioned. It is true that Westmorland and Somerset have a rather low birth-

rate, but Cornwall and Lancashire have an average birth-rate. At first sight this is all rather inconclusive, but some other data suggest that it is because the county as a whole is too large and its conditions too varied for one to reach any conclusions.

In *Whitaker's Almanack* for 1924 the birth-rate for 1921 is given for all the boroughs and cities of England, and for the urban districts with a population over 50,000. Over 300 towns are included in the list. In Lancashire, Sussex, Devon, Cornwall, and the West Riding of Yorkshire there are a large number of towns (5 to 11 in each) where the birth-rate is very low, 16 per thousand or less. In most other counties there is only one or at most two towns with such a low birth-rate.

The Welsh counties are small and contain relatively few towns, so that an equal number cannot be expected, but Carnarvon has 3, Cardigan 2, and Carmarthen, Pembroke, Montgomery, and Denbigh each one town with a birth-rate of 16 or under.

It cannot be coincidence that Lancashire and Yorkshire, Devon and Cornwall, Wales and Sussex, have certain places with these low birth-rates, for it is practically the same group of counties which was found to have a large amount of exophthalmic goitre.

The general geographical distribution of exophthalmic goitre, and its relationship to endemic goitre, make it likely that its incidence is mainly dependent on water-supply or other physical conditions. But the facts adduced here show quite clearly an association between a large amount of exophthalmic goitre and a low birth-rate.

The most likely explanation is that, where from social or industrial causes there are a large number of unmarried women or married women without children, the number of cases of Graves's disease will be increased.

Any other explanation cannot really be considered until the relationship of exophthalmic and endemic goitre has been more firmly established. This depends to some extent on the relationship of these two diseases to the water-supply, and this will be discussed in a later paper.

#### *Summary and Conclusions.*

1. Many of the facts discussed are difficult to summarize, and further evidence is needed before sure conclusions can be reached about the relationship of exophthalmic and endemic goitre.

2. The deaths which are recorded as from exophthalmic goitre in the Registrar-Generals' reports have a very definite geographical distribution.

Exophthalmic goitre in this sense is most common in Cornwall, Devon, and Somerset; in Wales (excluding the coal district in the south); in Westmorland and parts of Lancashire and Yorkshire; and in the southern counties of Scotland.

It is least common in three densely populated areas, Essex, Middlesex, and Hertford; Glamorgan and Monmouth; and Durham. Perhaps the west of

Ireland should be included, but the figures there may be very inaccurate owing to the disturbed state of the country. A map of its distribution in the British Isles is given.

3. The age incidence of these deaths and the high proportion in the country as compared with the towns are both similar to what is found in the Guy's Hospital cases of adenoma of the thyroid.

Apart from this, other evidence is that these deaths are mainly from true exophthalmic goitre rather than hyperthyroidism following adenoma. Statistics from hospitals in other parts of the country would be of great value in elucidating this.

4. Although certain areas of endemic goitre are well known, there is not sufficient evidence to construct a map as has been done for exophthalmic goitre.

The survey which is now being carried out by the Board of Education should make this possible, and until that is available it is wiser to defer any definite conclusions about the geographical relationship of endemic goitre and Graves's disease in England. As far as the evidence goes at present there seems to be a tendency for the two to occur in the same localities. If this actually is so, it is difficult to explain by what is at present known of the physiology and pathology of the thyroid.

5. In addition to geographical causes, there is evidence of other factors in the production of exophthalmic goitre. Where Graves's disease is unduly prevalent there is often a lower birth-rate.

Most likely the social and industrial factors which produce a low birth-rate cause secondarily a large amount of Graves's disease, where other conditions are favourable.

It is possible, but much less likely, that the water-supply or other physical conditions favouring the development of Graves's disease affect the women of the district as a whole, so that there is a lower birth-rate.

#### REFERENCES.

1. Baillarger, *Rapport de la commission d'enquête sur le goitre et le crétinisme en France*, Paris, 1873.
2. Hirsch, A., *Handbook of Geographical and Historical Pathology* (New Sydenham Society), Lond., 1885, ii. 121-202.
3. Berry, James, *Diseases of the Thyroid Gland*, Lond., 1901, 177.
4. Mackenzie, H., *Albutt and Rolleston's System of Medicine*, Lond., 1914, 2nd edit., iv. 361.
5. McCarrison, Robert, *The Thyroid Gland*, Lond., 1917, 195.
6. Wilks, Samuel, *Guy's Hospital Reports*, Lond., 1870, 3rd ser., xv. 46.
7. Campbell, J. M. H., *Quart. Journ. Med.*, Oxford, 1921-2, xv. 64.

8. Osler, Sir William, *Principles and Practice of Medicine*, Lond. and N. York, 1916, 8th edit., 872.
9. Hirsch, A., *loc. cit.*, Lond., 1885, 142.
10. McCarrison, Robert, *loc. cit.*, Lond., 1918, 83, 85.
11. Berry, James, *loc. cit.*, Lond., 1901, 57.
12. Stacey, W. W., *Report of School Medical Officer*, Cheshire, 1919.
13. Milligan, E. H. M., *ibid.*, Bath, 1919.
14. Turner, A. C., *ibid.*, Leicester, 1919.
15. Turner, A. C., *ibid.*, Leicester, 1920.
16. Ferguson, J. B., *ibid.*, Smethwick, 1920.
17. Sheasby, H., *ibid.*, Cardiff, 1920.
18. Eady, —, *ibid.*, Worcestershire, 1921.
19. Adkins, G., *ibid.*, Devon, 1921.
20. Paulasz, —, *ibid.*, Warrington, 1921.
21. Atlee, C. N., *ibid.*, S.E. London, 1922.
22. Tucker, S., *ibid.*, Kent, 1922.
23. Brewer, D., *ibid.*, Swindon, 1922.
24. Brewer, D., *ibid.*, Swindon, 1923.
25. Wheatley, J., *ibid.*, Shropshire, 1923.
26. Milligan, E. H. M., *ibid.*, Glossop, 1923.
27. Thomas, D. J., *ibid.*, Acton, Middlesex, 1923.
28. Moffatt, C. W. P., *ibid.*, Bolton, 1923.
29. McGonnigle, G. C. M., *ibid.*, Durham County, 1923.
30. Boul, W. T. G., *ibid.*, East Suffolk, 1923.
31. *Report of Physical Examination of Men of Military Age, 1917-18*, H. M. Stationery Office, 1919.
32. Adams, E. W., and Crossley, H. N., *Lancet*, Lond., 1923, ii. 501.
33. Coindet. Quoted by Marine, D., *Physiological Reviews*, 1922, ii. 531.
34. Huxley, J. S., 'Review on Sex Determination,' *Medical Science, Abstracts and Reviews*, Oxford, 1924, x. 109-111.
35. *Whitaker's Almanack*, Lond., 1924, 531.
36. *Water Undertakings of England and Wales* (Local Government Board Publication, 1915).
37. Kimball, O. P., and Marine, D., *Arch. Int. Med.*, Chicago, 1918, xxii. 41.
38. Kimball, O. P., and Marine, D., *Journ. Amer. Med. Assoc.*, 1919, lxxiii. 1873.
39. Berry, James, *Proc. Roy. Soc. of Med.*, Lond., 1921, 'Sect. Surgery,' xiv. 3, 94.

## APPENDIX

## DEATHS FROM EXOPHTHALMIC GOITRE

- Table 1. English counties.
- Table 2. Welsh counties.
- Table 3. London metropolitan boroughs.
- Table 4. English and Welsh county boroughs.
- Table 5. Scotland.
- Table 6. Ireland.
- Table 7. Summary.

In each table the first column gives the total number of deaths registered as from exophthalmic goitre, the second column gives the population in thousands, and the third column the 'index figure' for exophthalmic goitre, i. e. the number of deaths annually per million of population living.

In Tables 1-4 the deaths are for the seven years 1913-19 (for 1913-14 for the whole population, and for 1915-19 for the civilian population only). In Tables 1 and 2 the rural and urban districts are shown together because in general they gave very similar results, but the figures for the county boroughs are excluded and shown separately in Table 4.

In Table 5 the deaths are for the ten years 1911-20; the burghs are included with the counties, except in the case of Glasgow. In Table 6 the deaths are for the ten years 1913-22; the county boroughs are included with the counties, except in the case of Dublin and Belfast. The figures for 1913-21 were given for the whole of Ireland, but for 1922 for the Free State only, and the figures for the Ulster counties were obtained by taking the average of the previous nine years.

The population for Ireland is from the census returns for 1911; elsewhere the mean of the figures given for 1911 and 1921.

In Tables 5 and 6 the figures in brackets, after single counties, give the index figure for that county, where the population is below 100,000 and the county is therefore grouped with the adjoining one.

TABLE 1. *English Counties (excluding Hereford and Monmouth).  
Deaths from Exophthalmic Goitre 1913-19.*

Counties.	I. Total Deaths from Exoph- thalmic Goitre.	II. Popula- tion in Thou- sands.	III. Exoph- thalmic Goitre. 'Index Figure.'	Counties.	I. Total Deaths from Exoph- thalmic Goitre.	II. Popula- tion in Thou- sands.	III. Exoph- thalmic Goitre. 'Index Figure.'
Bedford	14	200	10.1	Middlesex	72	1,209	8.3
Berks.	16	196	12.0	Norfolk	28	323	13.6
Bucks.	18	224	11.3	Northants	17	214	19.3
Cambs.	10	130	10.7	Northumberland	38	337	14.3
Cheshire	68	611	15.4	Nottingham	37	360	14.3
Cornwall	55	329	24.6	Oxford	21	137	24.0
Cumberland	31	211	20.6	Shropshire	23	247	14.3
Derby	50	578	12.4	Somerset	56	393	22.3
Devon	62	448	21.7	Stafford	58	632	12.3
Dorset	14	227	9.4	Suffolk	31	322	14.8
Durham	56	970	8.6	Surrey	55	715	11.4
Essex	46	1,042	7.4	Sussex	44	247	16.0
Gloucester	30	330	13.3	Warwick	23	311	10.1
Hants *	45	535	12.0	Westmorland	11	62	27.1
Hertford	19	324	8.3	Wilts.	22	291	11.9
Huntingdon †	24	191	18.0	Worcester	20	293	10.1
Kent	94	1,042	13.1	Yorks. (E. R.)	25	156	23.4
Lancs.	218	1,741	18.6	Yorks. (N. R.)	40	205	20.0
Leicester	20	255	11.1	Yorks. (W. R.)	152	1,512	15.1
Lincoln	51	438	17.1				

\* Including Isle of Wight.

† With Rutland, Isle of Ely, and Soke of Peterborough.

TABLE 2. *Welsh Counties (with Monmouth and Hereford).*

Counties.	I. Total Deaths from Exophthalmic Goitre.	II. Population in Thousands.	III. Exophthalmic Goitre. 'Index Figure.'
Anglesea and Carnarvon	22	174	18
Denbigh and Flint	30	242	17.6
Radnor and Cardigan	20	81	35.3
Montgomery and Merioneth	17	97	25.0
Brecknock and Hereford	26	175	21
Pembroke and Carmarthen	31	256	17
Glamorgan	53	795	9.3
Monmouth	13	335	5.3

TABLE 3. *London.*

Metropolitan Boroughs.	I. Total Deaths.	II. Popula- tion in Thou- sands.	III. Annual Deaths per Million Living.	Metropolitan Boroughs.	I. Total Deaths.	II. Popula- tion in Thou- sands.	III. Annual Deaths per Million Living.
Battersea	11	166	9.4	Lambeth	20	294	9.7
Bermondsey	6	129	6.6	Lewisham	15	174	11.6
Bethnal Green	5	115	6.1	Paddington	6	144	6.0
Camberwell	12	285	6.0	Poplar	6	153	5.6
Chelsea	1	63	2.3	St. Marylebone	9	98	13.1
Deptford	7	115	8.7	St. Pancras	6	219	3.9
Finsbury	4	78	7.3	Shoreditch	4	98	5.9
Fulham	11	159	9.8	Southwark	7	180	5.6
Greenwich	9	102	12.5	Stepney	12	232	7.4
Hackney	17	225	10.7	Stoke Newington	4	50	11.4
Hammersmith	8	136	8.3	Wandsworth	18	333	7.7
Hampstead	13	91	21.7	Westminster	8	127	9.0
Holborn	2	39	7.3	Woolwich	7	136	7.3
Islington	18	336	7.6				
Kensington	18	164	15.7	Total for London	264	4,441	8.6



GEOGRAPHICAL DISTRIBUTION OF EXOPHTHALMIC GOITRE 221

TABLE 4. *English and Welsh County Boroughs.*

County Boroughs.	I. Total Deaths.	II. Popula- tion in Thou- sands.	III. Annual Deaths per Million Living.	County Boroughs.	I. Total Deaths.	II. Popula- tion in Thou- sands.	III. Annual Deaths per Million Living.
Barnsley	4	53	10.7	Liverpool	49	763	9.1
Barrow-in-Furness	3	65	6.6	Manchester	64	731	12.4
Bath	5	70	10.1	Merthyr Tydfil	6	88	9.7
Birkenhead	14	135	15.0	Middlesbrough	11	124	12.6
Birmingham	57	860	9.4	Newcastle	20	271	10.6
Blackburn	16	134	17.0	Newport (Mon.)	8	87	13.1
Blackpool	13	61	30.4	Northampton	4	90	6.3
Bolton	32	184	24.8	Norwich	7	123	8.1
Bootle	6	72	11.9	Nottingham	9	264	10.3
Bournemouth	13	83	22.3	Oldham	9	150	8.6
Bradford	27	290	13.3	Oxford	9	54	23.7
Brighton	14	133	15.1	Plymouth	22	172	24.7
Bristol	25	361	9.9	Portsmouth	16	241	9.4
Burnley	15	109	19.6	Preston	13	118	15.7
Burton-on-Trent	7	47	21.3	Reading	9	89	14.4
Bury	4	59	9.6	Rochdale	20	93	30.7
Canterbury	2	24	11.9	Rotherham	2	64	4.4
Cardiff	14	186	10.7	St. Helens	5	99	7.3
Carlisle	6	52	16.6	Salford	11	233	6.7
Chester	5	39	18.3	Sheffield	36	472	10.9
Coventry	9	115	11.1	Smethwick	3	74	5.7
Croydon	14	178	11.1	South Shields	4	110	5.1
Derby	11	125	12.6	Southampton	4	122	4.7
Dewsbury	6	53	16.3	Southend	8	80	14.3
Dudley	5	51	14.3	Southport	10	71	20.0
Eastbourne	8	54	21.1	Stockport	18	124	20.7
East Ham	4	143	3.9	Stoke-on-Trent	15	239	9.0
Exeter	6	60	14.3	Sunderland	4	152	3.7
Gateshead	7	118	7.7	Swansea	9	119	10.9
Gloucester	5	50	14.3	Tynemouth	4	60	9.6
Great Yarmouth	4	57	10.0	Wallasey	16	84	27.1
Grimsby	5	77	9.3	Walsall	3	93	4.6
Halifax	2	100	3.0	Warrington	5	74	9.6
Hastings	13	60	30.9	West Bromwich	3	69	6.1
Huddersfield	13	111	17.0	West Ham	6	294	3.0
Ipswich	7	75	13.3	West Hartlepool	5	64	11.1
Kingston-on-Hull	12	287	6.0	Wigan	5	90	7.9
Leeds	19	447	6.0	Wolverhampton	6	95	9.0
Leicester	14	231	8.6	Worcester	3	48	9.0
Lincoln	3	59	7.3	York	11	83	19.0

TABLE 5. *Scotland.*

No.	Counties.	I. Total Deaths.	II. Population in Thousands.	III. Annual Deaths per Million Living.
1	Shetland and Orkney (4), Caithness (23), Sutherland (10), Ross and Cromarty (11)	19	183	10.4
2	Inverness (14), Nairn (11), Moray (19)	21	140	15.0
3	Banff (7) and Aberdeen (7.5) (with Aber- deen City (7.0))	27	373	7.3
4	Kincardine (10), Forfar (10), and Fife (11) (with Dundee (10.7))	62	590	10.5
5	Perth (19), Kinross and Clackmannan (15)	30	163	18.4
6	Stirling	24	161	14.9
7	Dumbarton (8), Argyll (11), and Bute (8)	22	225	9.8
8	Renfrew (with Paisley (20) and Greenock (10))	40	279	14.0
9	Ayr	26	268	9.1
10	Lanark	56	452	12.4
11	Glasgow	109	1,036	10.6
12	West, Mid, and East Lothian (with Edin- burgh (13) and Leith (8))	74	631	11.7
13	Dumfries (11), Kirkcudbright (18), and Wigtown (32)	25	143	17.5
14	Berwick (27), Peebles (27), Selkirk (52), and Roxburgh (28)	37	117	31.6

TABLE 6. *Ireland.*

No.	Counties.	I. Total Deaths.	II. Population in Thousands.	III. Annual Deaths per Million Living.
1	Londonderry	12	140	8.6
	Antrim	12	194	6.2
	Belfast City	30	387	7.8
	Down (9) and Louth (6)	23	268	8.6
		77	989	7.8
2	Tyrone	14	143	9.9
	Armagh	14	120	11.6
	Monaghan (18) and Meath (11)	20	136	15.0
	Dublin	21	172	12.1
	Dublin City	42	304	13.8
		111	875	12.7
3	Wicklow (6.5) and Kildare (7.5)	9	128	7.0
	Queen's County (11), Carlow (11), and Wex- ford (11)	21	193	11.0
	Waterford (8) and Limerick (10)	21	227	9.2
		51	548	9.3
4	Cork	17	392	4.8
	Kilkenny (4) and Tipperary (5)	10	227	4.8
	King's County (5) and Westmeath (5)	6	117	5.1
	Cavan (4), Leitrim (5), and Fermanagh (6)	11	219	5.0
	Donegal	6	168	3.6
		50	1,123	4.5
5	Kerry (2.5) and Clare (1)	5	264	1.9
	Galway (3) and Mayo (1)	6	374	1.6
	Sligo (2.5), Roscommon (2), and Long- ford (2.5)	5	217	2.3
		16	855	1.9

# GEOGRAPHICAL DISTRIBUTION OF EXOPHTHALMIC GOITRE 223

TABLE 7. *Summary.*

Area.	I. Total Deaths.	II. Population in Thousands.	III. Annual Deaths per Million Living.
England and Wales. Rural districts	829	7,231	16.3
" " " Urban districts	1097	12,292	12.8
" " " County boroughs	934	11,865	11.2
" " " London	264	4,358	8.6
Scotland (excluding larger burghs)	360*	2,793	12.9
" Burghs: Edinburgh, Glasgow, Dundee, Aberdeen, Paisley, Leith, and Greenock	213*	2,028	10.5
Ireland	306*	4,390	7.0
North of Scotland (Groups 1-9)	—	2,382	11.4
Scotland, Industrial belt including Edin- burgh and Glasgow (Groups 10-12)	—	2,117	11.3
Scotland, southern counties (Groups 13, 14), and England north of (and including) Yorkshire (N. and E. Riding)	—	2,276	15.3
Yorks. (W. R.), Notts., Lincs., Huntingdon, Norfolk, and Suffolk	—	3,014	15.2
Lancs., Shropshire, and Cheshire	—	2,519	17.4
Wales, with Gloucester, Oxford, Somerset, Devon, and Cornwall	—	3,776	16.5
Other southern counties	—	3,316	12.4
Midland counties	—	2,876	11.4
Middlesex, Hertford, and Essex	—	2,443	8.0
London metropolitan boroughs	—	4,358	8.6
Ireland (East, Groups 1-3)	—	2,412	10.0
Ireland (West, Groups 4 and 5)	—	1,978	3.8†

\* Figures for 10 years; others for 7 years.

† Doubtful if this figure is reliable: see text.

## PROGRESSIVE LIPODYSTROPHY<sup>1</sup>

By W. N. BOOG WATSON AND W. T. RITCHIE

With Plates 8 and 9

PROGRESSIVE lipodystrophy is a rare disease characterized by symmetrical and progressive loss of subcutaneous fat over the face, neck, arms, thorax, and abdomen, with a relative or absolute abundance of subcutaneous fat over the lower limbs. The condition was first described by Barraquer (2) in 1906 in a woman aged 25, who became affected at the age of 18, and in 1907 by H. Campbell (9), whose patient was a woman, aged 21, in whom the disease began at the age of 7 years. In 1911 Simons (44) recorded a case in a woman, aged 21, in whom the dystrophy began at the age of 11, and he designated the disease lipodystrophia progressiva. Since then over fifty well-authenticated cases have been recorded, the greater proportion having been females and only seventeen males. Among the most exhaustive descriptions are those of Boissonnas (5), Smith (46), and Parkes Weber (51, 52).

### *Clinical Reports.*

*Case I.* (This case was briefly recorded in *Transactions of the Medico-Chirurgical Society of Edinburgh*, 1923-24, N.S., xxxviii. 78.) M. C., an unmarried woman, aged 24, of pure Scottish descent, a book-keeper, was admitted to the Royal Infirmary of Edinburgh on November 15, 1923, complaining of thinness of the face of twelve years' duration.

A full-time child, she was born with the aid of forceps. During infancy she suffered from measles, whooping-cough, and pneumonia. During the first twelve years of her life she was, her mother states, a healthy child, plump and well developed; this is borne out by photographs taken at that time. When she was 12 years of age she fell over the banisters, a height of one flight of stairs, and landed on her feet, apparently unhurt. At that time the mother first noticed a change in the appearance of the child's mouth, but she is of opinion that this began before the accident.

The change referred to was a falling in of the cheeks close to the angles of the mouth. After a few months this falling in had extended to the whole of both cheeks and to the temporal regions. The thinness of the face became so

<sup>1</sup> Received September 6, 1924.

marked that the girl was kept away from school for a year, and during that time she was admitted to the Royal Edinburgh Hospital for Sick Children under the care of Dr. John Thomson. She remembered that she was then said to be well proportioned from the neck downwards. During the two years following the onset of symptoms there was progressive, symmetrical wasting of the upper arms, then of the forearms, and eventually of the thorax and abdomen. The process was complete at the end of two years, namely at the age of 14. Since then the condition had remained stationary, so far as she and her relations knew. She had never been aware of any excessive adiposity of the lower limbs. Her home had been comfortable and healthy; her food had always been plentiful and good. Menstruation began at the age of 14; the periods had been regular. At no time had she experienced any weakness or loss of muscular power; she had always been able to follow her occupation, which is congenial and healthy; she was a keen lawn-tennis player, and could walk fifteen miles without distress. She had suffered from no illness, other than those previously mentioned in childhood. During the last three years she had been weighed every three months, her weight varying between 46.2 and 43.4 kg. During the last few years she had become increasingly sensitive with regard to her condition, especially the emaciation of the face, and she came to hospital in the hope that something might be done to improve this. As she had previously been under the care of Dr. John Thomson, we asked him to see her, and he recognized the disease as progressive lipodystrophy.

*Family history.* Her father died at the age of 46 of pulmonary tuberculosis, twelve years ago. Her mother was alive and healthy. The first child, a boy, was born at full time thirty years ago, and was killed during the late war. The cervix was lacerated during that birth, and was not repaired although the uterus was curetted, and a pessary was worn for six years. During this time five miscarriages occurred, at the 2nd, 4th, 2nd, 5th, and 4th months; M. C. was the first child born after those miscarriages. The next child, a girl, born two years later, was alive and healthy. Another girl, born two years later, died of meningitis at the age of 10 months. One year later a fourth daughter was born; she was now aged 19 and, although she had never menstruated, was otherwise healthy. All these children were delivered with forceps. The last pregnancy, seventeen years ago, ended as a miscarriage at the fifth month. There was no record of any wasting disease in the patient's family or among her collaterals.

*State on examination.* Height, 5 ft. 0 in. (152 cm.); weight, 95.84 lb. (43.44 kg.). The most striking feature was the appearance of the face. This was so haggard and emaciated as to suggest the last stage of a long wasting illness. The eyes were a little sunken; there was complete loss of subcutaneous fat over the face, the skin being deeply sunken over the temples and even more markedly over the cheeks. The hollow below each zygoma was divided obliquely by the prominent band of the zygomaticus muscle and partially filled posteriorly by the masseter muscle. Both sides of the face were equally affected. The nose was well shapen; the ears showed no stigmata of degeneration; the lips were rather prominent. The extreme thinness of the face, while the motor power of all the muscles of the face was perfectly preserved, differentiated the facies from that of a muscular dystrophy.

The neck was scraggy, with prominent sternomastoid muscles. The shoulders showed marked loss of subcutaneous fat, so that each bundle of muscle-fibres could be traced to its bony attachment. This was particularly well seen in the case of the deltoids. The wasting was seen throughout the upper limbs as far as the wrists, but the hands were not affected. The absence of subcutaneous fat, so marked over the face and arms, was also obvious over the thorax and abdomen (Plate 8, Figs. 1 and 2). The breasts were moderately full, but the fullness was due to glandular, not fatty, tissue. The mons veneris was much atrophied. On both sides the wasting extended down to the level of a line stretching roughly from the 5th lumbar spine to a point 10 cm. below the tubercle of the ilium and thence

to the fold of the groin. Below that level, and in striking contrast to the upper part of the body, there was an abundance of subcutaneous fat over both lower limbs. This was definitely in excess over the thighs and calves, and particularly over both right and left trochanteric regions (Fig. 2 and Table II). Above each knee, at the level of the lower border of the belly of the vastus medialis, was an annular groove which simulated the impression that might be caused by the tying of a piece of rope around the limb. Over the feet the subcutaneous tissue was in proportion to her height and weight. There was no oedema in any part of the body.

Over the whole body the *skin* was of a healthy colour, smooth, pliable but not unduly elastic, and neither too moist nor too dry. No unusual pigmentation was detected. The hair of the head and eyebrows was plentiful; axillary hair was present but not abundant; pubic hair was of normal amount and distribution. Nowhere was there any hypertrichosis. The nails were healthy.

The *muscles* were all well developed. Those of the shoulder girdles, upper arms, and forearms stood out clearly beneath the thin skin like those of an athlete. When she smiled the face became deeply wrinkled. No fibrillary twitching or myoidema was ever observed. The tone of the muscles was neither diminished nor increased; the motor power in all groups of muscles was good; the electrical reactions, galvanic and faradic, were normal.

The *bones* presented no deformity, and radiographic examination revealed no signs of their being atrophied, while the pituitary fossa was of normal size and shape. All the joints were healthy.

The appetite and digestion were uniformly good, yet there was a tendency to constipation. The teeth were regular and in good condition; the tongue was normal. Physical examination of the abdomen revealed no abnormality. The faeces were not excessive in amount and were of normal appearance. For three days the patient was given a calculated diet containing 132 grm. of fat *per diem*. A twenty-four hours' specimen of faeces was then examined. No steatorrhoea was detected. The fat estimation, performed by Mr. W. O. Kermack in the Research Laboratory of the Royal College of Physicians of Edinburgh, showed that the total fat in the faeces in twenty-four hours was 8.48 grm., this being 6.42 per cent. of the amount ingested; the percentage of fat in the dried faeces was 8.75, and 65 per cent. of the fat was split.

Both clinically and radiographically the *heart* was of normal form and size; the cardiac sounds were pure and clear; the cardiac rhythm was regular; the rate varied between 80 and 90 a minute; the electro-cardiograms were normal. The walls of the brachial, radial, and other palpable arteries were a little thickened; the arterial systolic pressure varied between 132 and 120 mm. Hg., the diastolic pressure being between 102 and 85 mm. Hg. The average blood-pressure was 125/85.

The *lymphatic glands* and *spleen* were not enlarged. The red blood corpuscles numbered 5,180,000, and the leucocytes 8,400 per c.mm. The polymorphonuclear leucocytes averaged 67 per cent., the small lymphocytes 25 per cent., and large mononuclears 8 per cent. The percentage of haemoglobin was 75. The Wassermann reaction of the blood was negative.

Physical and radiographic examination of the *respiratory system* revealed no signs of disease. The average amount of *urine* passed in 24 hours was 1,450 c.c. The urine contained no abnormal constituents. The urinary diastase test showed  $d = 6.6$  units.

The *menstrual periods* began at the age of 14; they were of twenty-eight-day habit, lasting for four days and accompanied by only slight discomfort. *Nervous system*: she was an intelligent woman of bright, cheerful disposition. There was no loss of motor power and no sensory disturbance. All the reflexes were normal; the cranial nerves were healthy. When the hands and fingers were outstretched a faint tremor could be observed in them. Dr. Laura M.



Ligertwood reported that there was a high degree of myopia but unaltered fields of vision.

The *thyroid* was not enlarged, and there were no signs of hyperthyroidism or hypothyroidism. The basal metabolic rate was +8 per cent. The response to adrenalin was tested by subcutaneous injection of 0.5 c.c. of 1:1000 solution. The effect on the rate of pulse and respiration and on the systolic and diastolic blood-pressures indicated that the response to adrenalin was of moderate degree. The external secretion of the pancreas was normal, as ascertained by examination of the faeces to which reference has already been made. Loewi's adrenalin test was negative. The percentage of fasting blood-sugar was 0.108, and while fasting the urine was sugar-free. After administration of 50 grm. of glucose the percentage of blood-sugar was 0.143 and 0.113 at the end of the first and second hour respectively. During the first hour after taking the glucose, 1.0 grm. of sugar was excreted; during the second hour, 1.04 grm.; during the third hour, 1.0 grm.; during the fourth hour, 0.27 grm. Thereafter the urine was again sugar-free.

*Case II.* Mrs. L., a Scot, aged 24, married, a primipara four months pregnant, was examined at the Edinburgh Royal Infirmary on February 20, 1924. She was a patient of Dr. Keppie Paterson's, and we are indebted to him for the opportunity of examining her. She considered herself to be in good health, though she knew that she was too thin.

A full-time, plump infant, she was healthy until the age of 6 years. She then suffered from measles, and soon after recovery therefrom both sides of her face became very thin, the cheeks especially falling in. She was admitted to the Royal Infirmary as she was thought to be suffering from 'consumption of the bowels'. It was then noticed that the wasting had spread from the face to the neck and shoulders. The condition became stationary at the age of 8. When aged 9 she suffered from 'inflammation of the brain', and since then she had been subject to headaches for periods of two or three weeks. Menstruation began at the age of 15 and was regular until the present pregnancy.

*Family history.* Her father, aged 49, and mother, aged 50, were alive and well. After their marriage two children were born; both died in infancy. Then followed a miscarriage. Mrs. L. was the next child; she was followed by two miscarriages and then by two brothers, now aged 21 and 19, who were healthy. Two children who died in infancy were then born, and finally a sister, now aged 13, who was healthy. The patient's husband, aged 36, was alive and well. There was no record in the family of any condition similar to that from which the patient suffered.

*State on examination.* Height, 5 ft. 2 in. (157 cm.); weight, 105½ lb. (47.74 kg.). She was a bright, intelligent woman. The face was haggard, with marked hollowing of the cheeks and temporal regions (Plate 9, Fig. 3), but all the facial muscles were well developed and contracted normally. The absence of subcutaneous fat was well marked, not only in the face, but also in the neck, chest, abdomen, and arms. The hands were unaffected. The muscles of the upper extremities and upper part of the trunk were well developed; the muscle-bundles and bony attachments were clearly distinguished, particularly over the shoulders. The absence of subcutaneous fat ceased at the same level as in Case I, namely, at that of a line passing from the 5th lumbar spine to the groin and passing 10 cm. below the tubercle of the ilium. Below that level there was a superabundance of subcutaneous fat, symmetrically distributed and without any localized accumulation. Behind each knee there was a well-marked horizontal sulcus. The increase of fat ceased at the ankles, the feet being unaffected. The skin was smooth and supple, not unduly elastic; the hair of the scalp was plentiful, but there was no hypertrichosis. The digestive system and lungs were healthy. The heart was of normal size, its sounds were pure and clear; the pulse was regular,

its rate was 82 per minute; the systolic and diastolic blood-pressure were 128 and 78 respectively. The red blood corpuscles numbered 4,700,000 and the leucocytes 7,600 per c.mm.; the haemoglobin percentage was 90; the Wassermann reaction of the blood was negative. The urine contained no abnormal constituents. Radiographic examination revealed no atrophy of the bones, while the pituitary fossa was of normal shape and size. There was a considerable degree of scoliosis. On June 30, 1924, she was delivered of a plump, healthy baby.

*Case III.* Mrs. E. W., a Scot, aged 38, came under observation on February 27, 1924. We are indebted to Mr. F. E. Jardine, who recognized the nature of the disease, and to Dr. Louw for recommending her to come to the Royal Infirmary.

A full-time child, she contracted measles and whooping-cough in infancy. Until the age of 9 years she was plump and healthy; she then developed an abscess in the right side of the neck which was treated satisfactorily. Shortly thereafter it was noticed that she was becoming thin, and she believes that the thinness began in the face. Later the wasting spread to the neck, thorax, arms, and abdomen, but became stationary at the eleventh year. Menstruation began at 16, and had always been regular and accompanied with but little discomfort. She married at the age of 19. Three years later, before the first confinement, she was laid up in bed for several weeks by an illness that she refers to as 'shakings and rheumatics'. After the birth of the child the thinness of the face and trunk became more marked. The appetite had always been good, but during the last few years she had been troubled with indigestion. Her friends often urged her to seek medical advice on account of her thinness, but she paid little heed to the condition and felt well and able to do her work. Two years ago she noticed that her thinness was again becoming more pronounced. Six months ago she observed that the girth of the legs below the knees was increasing, and she and her husband noticed a pad of fat developing on the medial surface of each thigh a little above the knee.

*Family history.* Her father, a carter, aged 65, and mother, aged 60, were both alive and healthy. The patient, the eldest of the family, had six sisters and two brothers, all of whom were alive and well. Her husband, a miner, was healthy. She had two sons: one, aged 16, was a premature baby, the second was aged 14; both were healthy lads. She had not had any miscarriages. There is no record of any condition similar to her own in the family.

*State on examination.* Height, 5 ft. 2 in. (157 cm.); weight, 104 lb. (47.17 kg.). She was of average intelligence and not of nervous temperament. The face was sharp-featured with complete absence of subcutaneous fat; the cheeks were sunken and the hollow of each was divided obliquely by the zygomaticus muscle (Fig. 4). The neck was scraggy. The absence of subcutaneous fat extended down the arms, but not over the hands, and over the back and front of the thorax, abdomen, buttocks, trochanteric regions, and thighs. On the *outer* side of each thigh, at a level 9 cm. above the upper edge of the patella, there was a striking change, the subcutaneous fat below this level being plentiful. On the *medial* surface of each thigh, over the tendon of the adductor longus, was a localized accumulation of subcutaneous fat the size of the palm of an adult hand; with the exception of these two fatty masses there was an absence of subcutaneous fat over the anterior medial and posterior surfaces of the lower limbs as far down as the garter mark just below the tuberosity of the tibia. At this level there was a marked change, the legs being plump and the feet also presenting an excess of subcutaneous fat (Fig. 5). There was no oedema in any part of the body. The skin was smooth, supple, and neither too moist nor too dry. The dorsal surfaces of the forearms and hands were sunburnt, and there was slight hypertrichosis over the pigmented areas. The nails were healthy; on the scalp, eyebrows, pubic region, and axillae, the hair was of normal quantity and

texture. There was no localized sweating. The *muscles* were well developed, the muscle bundles and fibres being readily distinguished, though not so clearly as in our first case. The tone of the muscles was neither diminished nor increased, and there was no fibrillary twitching. Clinically and radiographically, the *bones* were healthy.

The appetite and digestion were good. The teeth in both jaws were replaced by dentures. The tongue was normal. There was no constipation or diarrhoea. While the patient was taking a mixed diet containing 132 gm. of fat *per diem* the faeces, which were of normal colour and consistency and presented no steatorrhoea, were subjected to analysis in the Research Laboratory of the Royal College of Physicians of Edinburgh. The weight of dried faeces passed in twenty-four hours was 5.3 gm.; the total fat was 1.17 gm. (22.2 per cent.), and of this 42.55 per cent. was split.

The patient did not complain of any subjective symptoms referable to the *circulatory system*. The heart was moderately enlarged, the apex-beat lying in the fifth left intercostal space  $4\frac{1}{2}$  in. from the mesial line; a soft systolic murmur was localized to the mitral area. Electrocardiographic records showed a normal rhythm with moderate degree of left ventricular preponderance. The arterial walls were soft; the pulse-rate was 78 per minute. The arterial systolic pressure was 138, the diastolic pressure 78 mm. Hg.

The *spleen* and *lymphatic glands* were not enlarged. The red blood corpuscles numbered 4,620,000 and the white cells 6,000 per c.mm.; the haemoglobin was 80 per cent. A stained blood-film revealed no abnormality. The Wassermann reaction of the blood was negative. Physical examination of the *respiratory system* revealed no indication of disease, although radiographic examination showed slight diminution of diaphragmatic movement and some increase of peribronchial and perivascular fibrous tissue on the right side. The *urine* measured 1,050 c.c. in 24 hours, and did not contain any abnormal constituents. Menstruation was regular, and not attended by dysmenorrhoea or menorrhagia.

*Nervous system.* She was of average intelligence, cheerful, and placid. She complained of occasional headaches and lassitude. There was no loss of motor power and no sensory disturbances; all the reflexes were normal; the cranial nerves were healthy. We are indebted to Dr. J. V. Paterson for reporting that the visual acuity, fundus oculi, and fields of vision were normal.

The *thyroid* was not enlarged and no signs of functional disturbance of the gland were detected. The basal metabolic rate was +8 per cent. The pituitary fossa was of normal size and shape, but it was almost completely roofed. The response to adrenalin, tested by a subcutaneous injection of 0.5 c.c. of a 1:1,000 solution, was of moderate degree. The adrenalin injection did not induce glycosuria, and Loewi's adrenalin test was negative.

When readmitted to hospital, on July 16, the patient said that the headaches had increased in frequency and severity, the weight had increased to 109 lb. (49.4 kg.), but the lack of subcutaneous fat in each trochanteric region (Fig. 5) was even more striking than it had been five months previously.

#### Discussion.

Progressive lipodystrophy is a disease without any particular racial incidence, and is not familial, hereditary, or congenital.

The relative frequency of the disease in the female sex has been emphasized by all writers on the subject. Indeed until 1914, when Husler (25) recorded two cases in boys, 10 and 9 years old respectively, the disease was thought to be peculiar to the female sex. Prior to 1914, however, male cases had been

observed by Shaw (43), Bury (8), and Hertz and Johnson (21), and since that year eleven further male cases, making a total of seventeen, have been reported (Table I). Nevertheless, there is still a marked disparity between the incidence of the disease in males and females, and this is not entirely explicable either by the greater sensitiveness of women to change and peculiarity of facial appearance or to the male mode of dress concealing excessive adiposity of the lower limbs.

TABLE I. *Progressive Lipodystrophy, Male Cases.*

	Date.	Recorded by	Age at Onset.	Age when observed.	Distribution of Lipodystrophy.
1	1905	Shaw, H. Batty	7	10	Face only
2	1912	Bury, J. S.	?	Boy	Face
3	1913	Hertz, A. F., and Johnson, W.	24	26	Face only
4	1914	Hertz, A. F., and Johnson, W.	37	38	Face. Chronic plumbism
5	1914	Husler, J.	6	10	Face only
6	1914	Husler, J.	6½	9	Face, neck, and upper part of thorax
7	1916	Gerstmann, J.	10	32	Face, neck, upper limbs, and trunk down to inguinal folds
8	1916	Gerhartz, H.	6	29	Face, neck, upper limbs, and trunk; and anterior surfaces of thighs
9	1917-18	Weber, F. Parkes	8	13	Face, neck, and trunk
10	1917-18	Weber, F. Parkes	9	11½	Chiefly the face
11	1918	Weber, F. Parkes	37	39	Face
12	1919	Boissonnas, L.	5	6	Face and neck
13	1921	Klien, H.	5	8	Face, arms, and upper part of trunk. Normal below pelvis
14	1922	Feer, E.	4 or 5	9	From face to feet. Two lipomas on back
15	1922	Irving, G. R.	8½	13	Face and neck. No mention of lower limbs
16	1922	Christiansen, V.	?	40	Face, neck, upper arms, and lower limbs
17	1922	Schwenke, J.	? 8	11	Face and upper part of body. Moderate excess of fat in lower part of trunk and in lower limbs

It is undoubtedly more frequent than would appear from the scanty number of cases on record, and lesser grades of the disease are liable to escape recognition or to be misinterpreted. A lady, aged 37, who came under our observation recently, had as a schoolgirl been known as 'Fatty'. When 33 she suffered from a 'nervous break-down' and the face, neck, arms, thorax, and abdomen became very thin, while the lower limbs retained their natural plumpness. Special dietetic treatment raised her weight from 112 lb. to 142 lb., and the face and other lean parts are said to have become temporarily fatter. Subsequently she was treated for ulceration of the stomach, appendicitis, intestinal adhesions, uterine fibroids, pulmonary tuberculosis, and neuro-circulatory asthenia. When seen by one of us she complained solely of the last-named disorder, but she knew of 'the great difference between the upper and lower half of the body', and her appearance was characteristic of progressive lipodystrophy.

*Age incidence.* The first signs of the disease are usually observed between the ages of 5 and 8 years (64.1 per cent.). The earliest recorded age of onset is 2 years (Trömner (49)), the latest is 37 years (Hertz and Johnson (22) and Weber (52)). The active stage of the disease, during which the lipodystrophy is progressive, usually lasts for two to three years, but it may last for a few months only or may extend to four years (Pic and Gardère (40)). The active stage having ended, the lipodystrophic process becomes stationary; its recrudescence is most exceptional, recovery is unknown. In one of Christiansen's cases the lipodystrophy of the face was renewed after erysipelas (10), and in our third case, activity having ceased at the age of 11, renewed wasting occurred at the age of 22, after her first pregnancy, and again at the age of 36 without obvious cause.

Most frequently the patients have come under observation between the ages of 9 and 11 years (eleven cases) or between 20 and 30 (twelve cases). The youngest patient when observed was a boy aged 4 (Trömner (49)), the oldest a man aged 40 (Christiansen (11)).

In the vast majority of cases the antecedent health has been good, and the first indication of the disease is progressive thinness of both sides of the face, coming on without any apparent cause and while the general health remains good. Medical advice is sought because the patient, becoming so thin, is suspected to be suffering from tuberculosis or other wasting disease; she may come for the express purpose of having the gross leanness of the face remedied; or the disease is first recognized when the patient consults her doctor for some independent affection. The hollowing of the temples is striking, that of the cheeks is even more pronounced, this being largely due to disappearance of the subcutaneous buccal fat. The orbital fat persists in some cases, in others it disappears. The lipodystrophy may remain localized to the face, as in the male cases recorded by Shaw (43), Hertz and Johnson (21, 22), one of Husler's (25), and one of Parkes Weber's (52) cases. The lipodystrophy, however, usually spreads to the neck, upper arms, forearms, thorax, and abdomen. The hands are almost invariably unaffected, but in Smith's case (46), a woman aged 30, they were involved slightly. The wasting seldom extends below the level of the brim of the pelvis. In three male cases the lipodystrophy involved the lower limbs: the anterior surfaces of the thighs in Gerhartz's case, aged 29 (17); the lower limbs in Christiansen's case (11), a man aged 40; and in Feer's case, a boy aged 9 years, the lipodystrophy extended from the face to the feet (15). In our third case the lower limit of the lipodystrophic process was about the level of the knees.

Below the level of the lipodystrophy the amount of subcutaneous fat is either normal or, more often, greatly increased. In the latter case the patient may have been unaware of the adiposity and therefore does not know in which region it developed first. The gluteal regions and that over each great trochanter, however, usually become markedly prominent, and the adiposity also involves the rest of the thighs, the legs, and the ankles, but rarely involves the feet. The



adiposity of the lower limbs usually develops later than the lipodystrophy of the face, arms, and trunk, but the two processes may be concurrent, as in the case recorded by Laignel-Lavastine and Viard (32). In two of Christiansen's cases (10), young married women, adiposity of the lower limbs was the first sign of the disease.

TABLE II. *Progressive Lipodystrophy. Circumferential Measurements in Centimetres.*

	Personal Cases.			Herrman's Case.	Smith's Case.	Jolowicz's Case.	Meyer's Case.	Strauch's Case.	Myxoedema. Height 5 ft. 3½ in. (160 cm.), Weight 11 st. 1 lb. (70.3 kg.).	Control. Height 5 ft. 1½ in. (156 cm.), Weight 7 st. 10½ lb. (49.2 kg.).
	1.	2.	3.							
Neck	28.1	31.1	32.2	31.5	28.5	—	—	29.5	34.0	30.5
Upper arm, right	17.5	20.1	21.1	22.0	21.5	23.5	—	25.0	28.8	23.0
left	17.0	19.8	19.2	—	20.0	22.0	—	—	28.8	21.5
Forearm, right	19.9	20.8	22.4	21.5	21.0	23.0	—	—	26.8	21.0
left	19.5	20.5	21.0	—	21.0	22.0	—	—	25.8	21.0
Wrist, right	14.4	14.2	14.9	—	13.5	—	—	—	16.0	15.5
left	14.0	14.2	14.4	—	13.7	—	—	—	16.5	15.8
Thorax level of nipple,										
full expiration	73.0	75.0	79.0	80.0	77.0	79.0	69.0	—	91.0	78.5
full inspiration	77.0	78.0	81.5	—	—	—	—	—	94.0	84.0
Abdomen, 2.5 cm.	67.0	*	61.0	—	58.5	65.0	—	—	89.3	67.0
above umbilicus										
Buttocks, at level of	82.0	91.8	86.0	62.0	85.5	97.0	106.0	90.0	99.0	85.0
great trochanter										
Thigh, 15 cm. above										
upper edge of patella,										
right	42.5	44.5	43.7	53.5	49.5	—	—	—	49.5	37.0
left	42.5	44.5	44.3	—	48.5	—	—	—	48.8	39.0
Leg, right calf	33.5	31.8	32.5	37.5	31.5	—	38.0	42.0	32.6	28.0
left calf	34.5	32.4	32.2	—	32.5	—	38.0	—	33.5	28.0
Ankle, right	23.0	22.5	23.2	23.0	19.0	—	—	24.0	21.0	18.8
left	23.0	22.5	23.4	—	19.0	—	—	—	22.7	19.0

\* Pregnant.

The marked difference between the girth of the lipodystrophic upper limbs and that of the adipose lower limbs is shown by the circumferential measurements in our three cases, and in others previously recorded (see Table II), and by the thickness of a fold of skin and subcutaneous tissue in different parts of the body, as indicated in Table III. Christiansen's differentiation of cases into two groups, those in which loss, and those in which excess, of subcutaneous fat is the chief sign, seems to be too arbitrary, as all degrees of transition have been recorded. The clinical features, although distinctive in children, become more pronounced in adolescents, and most striking in adult women. The most extreme case is probably that of which illustrations are shown in Meyer's (37) paper,



while the most vivid word-picture of a typical case is that given by Parkes Weber (50): 'One need only imagine a grotesque figure, the lower part of which seems to be modelled after an extraordinarily florid Venus of the "ultra-Rubens" style, whilst the face and upper part of the trunk might . . . bring to mind the popular idea of one of the witches in *Macbeth*.' The adiposity of the lower limbs was symmetrical in all recorded cases with one exception, namely, that of Laignel-Lavastine and Viard (32), in which the lower limb and labium minus were larger on the left than on the right side.

TABLE III. *Thickness in Millimetres of Fold of Skin and Subcutaneous Tissue.*

	Personal Cases.			Smith's Case.	Bossert-Rollett's Case.	Strauch's Case.	Myxoedema. Height 5 ft. 3½ in. (160 cm.). Weight 11 st. 1 lb. (70.3 kg.).	Control. Height 5 ft. 1½ in. (156 cm.). Weight 7 st. 10½ lb. (49.2 kg.).
	1.	2.	3.					
Cheek	2.8	3.0	2.8	3.5	4.0	—	18.2	13.4
Hand, dorsum	2.2	2.4	2.5	—	—	—	2.6	2.4
Forearm, right	2.2	2.0	1.8	3.0	2.1	—	13.6	5.0
left	2.2	2.0	1.8	2.0	—	—	15.0	6.4
Upper arm, right	2.8	2.2	2.0	3.0	2.5	10.0	14.6	6.4
left	2.8	2.2	2.0	2.5	—	—	14.0	8.0
Thorax, anteriorly	2.6	3.6	3.0	—	3.0	3.4	16.6	6.6
interscapular region	4.0	4.4	4.0	4.0	5.0	5.8	15.8	11.2
Lumbar region	3.6	—	4.4	5.0	—	—	17.4	12.0
Abdomen	3.8	2.4	3.2	4.0	—	20.25	26.0	14.0
Buttock	6.0	11.6	4.8	40.0	—	—	19.8	19.2
Thigh, 15 cm. above upper edge of patella, right	11.8	13.6	2.3	—	15.0	9.5	28.0	12.8
left	11.8	13.6	2.3	—	—	—	25.6	12.8
Leg, over anterior aspect of tibia, right	11.6	12.0	11.0	—	13.0	—	6.4	5.4
left	12.2	14.0	11.3	—	—	—	6.0	4.8
Ankle, right	9.0	—	5.0	—	—	—	5.2	4.0
left	9.0	—	5.5	—	—	—	5.2	4.0
Foot, dorsum	2.6	—	3.1	—	—	—	4.8	2.4

The skin is of normal colour, soft, smooth, and pliable. It has been suggested that some of the indiarubber-faced or elastic-skinned men, who may be seen in the side-shows of fairs, are cases of progressive lipodystrophy. But according to Smith (46) 'elastic skin' is a definite entity in which there is a pathological change in the elastic fibres without alteration of the other tissues of the skin. The skin appendages are usually normal, the hair being plentiful and the secretions normal in amount. Klien's case (30), a boy aged 8, presented hypertrichosis of the face, and the same change affecting the forearms, wrists, and dorsal surfaces of the hands was shown in one of Boston's cases (7), a woman aged 31, in whom

the lipodystrophy began between the ages of 12 and 15. In our third case there was slight hypertrichosis of the dorsal surfaces of the forearms, hands, and first phalanges. The secretion of sweat following pilocarpine was as plentiful over the lipodystrophic as over the more adipose parts of the body (Feer (14)).

Histological examination of the skin and subcutaneous tissue excised from lipodystrophic areas in four patients has revealed uniform changes (Simons (45), Christiansen (11), Feer (14), and Smith (46)). The skin was found to be normal in structure, but there was almost complete absence of fat in the tissue under the corium. Fat globules persisted in the sebaceous glands. A post-mortem examination has been recorded in only two cases. One of Husler's patients (25) developed progressive lipodystrophy when he was 6 years old and died six or seven years later of cerebro-spinal meningitis. The second case is that of Parkes Weber and Gunewardene (54), a girl who developed progressive lipodystrophy at the age of  $7\frac{1}{2}$  years, and died of pyaemia at the age of 13. In both these cases there was an absence of subcutaneous fat in the lipodystrophic region, but the amount of fat within the cavities of the body was not abnormal, and in the last-mentioned case the thyroid, ovary, adrenal, and pituitary were healthy.

In all cases the *muscles* are well developed and the patient often affirms that she is stronger than other women. In the lipodystrophic parts the individual muscle-fibres and their attachments stand out as clearly as those of a highly trained athlete, and although there is no hypertrophy of the muscles, those of the upper limbs and trunk appear to be enlarged because of the loss of subcutaneous fat which, in health, conceals to some extent the contour and contractions of the muscles. The tone of the muscles and their electrical reactions are normal.

The *bones* are not affected. The clinical and radiographic evidence on this point is conclusive, and affords a clear distinction between progressive lipodystrophy and bilateral facial hemiatrophy. Mention may here be made of Frank's case (16), a girl aged 11, who was also the subject of fragilitas ossium and blue sclerotics; several members of her family had presented blue sclerotics, deafness, and undue liability to fractures. The *cardio-vascular system* has been healthy in almost every instance. Frank's case (16) had a congenital heart lesion, and Smith's case (46), a woman aged 30, showed cardio-vascular changes secondary to chronic nephritis. Our third case had a slight degree of incompetence of the mitral valve with electrocardiographic evidence of predominant hypertrophy of the left ventricle. The *blood* has been normal in all cases, except in that of Smith (46), which had a consistent leucocytosis of 12,200 per c.mm. That incidental disease of the *respiratory tract* should occasionally be found is to be expected. Laignel-Lavastine and Viard (32) found signs of phthisis in their patient, a woman aged 39, but clinical and radiographic examination in other cases has yielded negative results. The *alimentary system* is healthy; and physical examination of the nervous system fails to reveal any abnormality except in so far as some of the patients are highly sensitive of their facial peculiarity.

*Aetiology.*

Campbell (9) suggested that the subcutaneous fat was drained away by over-activity of the sebaceous glands. Histological examination indicates that fat is still present in these glands, but over-activity of sebaceous glands has not been recorded in any case subsequent to that of Campbell. Laignel-Lavastine and Viard (32) were of opinion that an attenuated tuberculous infection was the causal factor in their case, but there has been no evidence of tuberculosis in other cases. Syphilis has been accused, but acquitted on both clinical and serological evidence. Christiansen (11) inclines to the view that lipodystrophy and muscular dystrophy are closely allied affections, and Simons (45), who alludes to the former as 'the sister of the muscular dystrophies', points out that in the latter disease there may be loss of adipose, as well as of muscular, tissue. This statement is suggestive, and although all writers lay stress on the fact of lipodystrophy being unaccompanied by wasting of any other tissue, we should bear in mind the possibility of a common cause for the atrophy of tissues, be it skin in scleroderma, fat in lipodystrophy, skeletal muscle in the myopathies, or elastic tissue in indiarubber-faced men.

Progressive lipodystrophy is certainly not due to malnutrition, and as corroborative evidence we have the results of over-feeding experiments in the cases of Mirallié and Fortineau (38) and Hartenberg (19). Their patients developed a great increase in size of the already adipose lower limbs, whereas the lipodystrophic upper parts of the body remained lean. Treatment by subcutaneous injections, in the one case of paraffin and in the other of a mixture of suet and human fat, was carried out by Campbell and by Holländer (23); in each patient the benefit obtained was only temporary. The fat assimilation in our first case was not disturbed. In our third case the percentage of split fat in the stool, being below 60, suggests some deficiency of the external secretion of the pancreas.

With regard to a possible error in fat metabolism, attention is drawn to the universal absence of steatorrhoea, to Simons's (44) observation indicating no increase of the blood lipase, and to Feer's (14) that lipaemia did not ensue after ingestion of 200 grm. of 20 per cent. cream. Carbohydrate metabolism has been investigated by several writers. The glucose tolerance was good in Spear's case (47), a girl aged 15; 40 grm. of galactose were fully utilized in Klien's case, a boy of eight years (30); the blood-sugar curve was normal in the cases reported by Feer (14) and Smith (46); in our first case the blood-sugar curve was normal, but the renal threshold for glucose was low, as there was a temporary glycosuria after 50 grm. of glucose. Alimentary glycosuria was observed in Gerhartz's (17) and one of Weber's cases (50). There was no glycosuria after adrenalin in the patient tested by Feer (14), nor in our first and third cases.

Frank (16) attributes the disease to a developmental error of the mesenchyme, and on this basis he links up progressive lipodystrophy with the osteogenesis imperfecta and congenital heart lesion in his case, a girl aged 11. On the same

hypothesis Blegvad and Haxthausen (3) correlate the osteogenesis imperfecta of their patient, who was not lipodystrophic, with a zonular cataract and atrophica maculosa cutis.

Disturbance of the endocrine glands has naturally been postulated in explanation of progressive lipodystrophy. In respect of the pituitary, no case has presented any signs of acromegaly or of interference with the optic tracts. Klien's patient (30) showed polyuria, enuresis, and rhinorrhoea, all of which responded to treatment with pituitary extract. Oliguria was noted in Gerhartz's case (17). In a number of cases (Simons, Cohn, Feer, Klien, Herrman, Smith, Husler, Christiansen, Reuben and Zamkin, and our three cases) the pituitary fossa was examined radiographically. In one of Christiansen's patients a small pituitary fossa was noted; in a second patient, who was also myxoedematous, the pituitary fossa was large; but in all other cases the fossa was of normal form and size. Simons (45) thought that the *thyroid* might be responsible, and a few cases have been recorded in which there was concurrent disease of the thyroid. Myxoedema was noted in one of Christiansen's cases (10), exophthalmic goitre in that of Smith (46) and that of Hartenberg (19), a tumour of the right lobe of the thyroid in Strauch's case (48). The basal metabolic rate was normal in Simons's case, and in the two of our cases in which it was estimated (Nos. 1 and 3); its acceleration in Smith's case (46) was due to hyperthyroidism, and in Boston's case probably to excitement (7). The thyroid was proved to be healthy by post-mortem examination in the case recorded by Parkes Weber and Gunewardene (54); and in no case has thyroid therapy been of value. In no instance, with the possible exception of our third case, was there any alteration of the faeces such as would suggest deficiency of the external secretion of the *pancreas*, while the estimations of sugar in the blood and urine, to which reference has been made, indicate that the internal secretion of the gland is not at fault. Moreover, Loewi's adrenalin test has been consistently negative, and the urinary diastase in our first case was normal. As regards the *sex glands*, there is no alteration in the onset, cycle, or duration of menstruation. That sexual function and desire are normal is shown by the number of cases occurring in married women, several of whom, including two of our cases, have given birth to one or more healthy children. There is nothing in the appearance of the female patients suggesting male sexual characteristics, but the distribution of the lipodystrophy resembles that occurring in some women after the menopause, while the adiposity affects those regions where abundance of subcutaneous fat is a secondary female sexual characteristic.

Simons (45) considered that although dysthyroidism was the chief cause there was an accompanying nervous factor. Christiansen (10) also suggests that the disease is of nervous origin. He points out that some of the cases present psychical changes in the direction of melancholia or anxiety neurosis. It is most probable, however, that any such change is an effect, and not the cause, of the disease, and the majority of the patients are certainly bright, alert, and intelligent. In a few instances the onset of progressive lipodystrophy has

been preceded or accompanied by a severe mental shock. One girl, aged 4, who also showed nystagmus and a tic, had been frightened by horses in a stable (Bossert-Rollett (6)); a boy aged about 8 had fallen through the ice (Gerhartz (17)); our first case had fallen over a flight of stairs, but this accident occurred after the lipodystrophy had begun.

The general appearance and characteristics of the patients do not correspond to either the vagotonic or sympathotonic types described by Eppinger and Hess. There is certainly no over-activity of the sympathetic component of the autonomic nervous system. The response to adrenalin in the two of our cases in which it was tested (Nos. 1 and 3), in one of Feer's cases (14), and in that of Klien (30), was of moderate degree, and there was no adrenalin glycosuria in these cases, nor in that of Simons (44).

Klien (30) suggests that the fault lies primarily in the pineal. This body, he states, normally undergoes involution about the same age at which progressive lipodystrophy develops; an abundance of nerve-fibres are said to unite the pineal to 'a subthalamic fat-regulating centre', and Klien considers that excessive localized atrophy of the pineal produces irregular function of that centre and ultimately disappearance of fat in certain areas of the body. The increase of subcutaneous fat over the lower part of the body is regarded as a secondary female sexual characteristic, developing at puberty and aided by an excess of fat-building material in the blood-stream. The chief pathological conditions known to affect the pineal are tumours and traumatic lesions, the latter occurring almost exclusively in male subjects. The clinical features of pineal lesions are as yet ill defined, and secondary pressure symptoms complicate those caused by damaged function of the gland. The clinical characteristics of progressive lipodystrophy, however, do not conform to those constituting the pineal syndrome, namely, precocious sexual development, excessive growth in height, generalized adiposity, hypertrichosis, and somnolence. Experimental research has corroborated the relation of these changes with disease of the pineal (Luce (36), Izawa (27)).

Parkes Weber (53) considers progressive lipodystrophy to be 'a redistribution of fat (glycerine esters) in the subcutaneous tissue of the body analogous to the redistribution of pigment in the skin in vitiligo . . . due to hidden disturbance in the vegetative nervous system'. The analogy is certainly an apt one. Some disturbance of the trophic nerve-supply is suggested not only by the distribution of the dystrophy but also by the co-existence of other trophic changes in some cases (Jolowicz (29), Gerhartz (17), Feer (14), Klien (30)). The persistence of one or more lipomas in the parts otherwise lipodystrophic (Christiansen (10), Feer (15)) might be explained by the absence of any trophic nerve-supply to the neoplasms.



*Conclusions.*

The clinical features in our three cases conform with those of other cases previously published. We have failed to find any condition that would explain the pathology of the disease. All researches regarding assimilation, metabolism, the functions of the endocrine glands and of the autonomic nervous system, have failed to lighten the darkness which enshrouds the aetiology of progressive lipodystrophy. The cause of the loss of subcutaneous fat in the upper part, and of adiposity in the lower part, of the body still remains an unsolved riddle. The loss of subcutaneous fat is not due to temporary atrophy, but to permanent failure on the part of the fat-cells of the subcutaneous tissue to synthesize fat. The cause of this failure is probably of nervous, not of endocrine, origin.

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## REFERENCES.

1. Babonneix, L., *Bull. et Mém. Soc. méd. d. Hôp. de Paris*, 1923, 3<sup>e</sup> sér., xlvii. 29; *Progrès méd.*, 1923, 24.
2. Barraquer, L., *Abstr. in Neurol. Centralb.*, Leipzig, 1907, xxvi. 1072.
3. Blegvad, O., and Haxthausen, H., *Brit. Med. Journ.*, 1921, ii. 1071.
4. Boissonnas, L., *Rev. méd. de la Suisse romande*, Genève, 1914, xxxiv. 214.
5. Boissonnas, L., *Rev. neurol.*, Paris, 1919, xxxv. 721.
6. Bossert-Rollett, *Monatschr. f. Kinderheilk.*, Leipzig, 1918, Orig., xiv. 230.\*
7. Boston, L. N., *New York Med. Journ. Rec.*, 1923, cxviii. 668.
8. Bury, J. S., *Dis. of the Nerv. System*, Manchester, 1912, 267, Fig. 102.
9. Campbell, H., *Trans. Clin. Soc., Lond.*, 1907, xl. 272; *Proc. Roy. Soc. Med., Lond.*, 1912-13 (Neurol. Sect.), vi. ii. 71.
10. Christiansen, V., *Rev. neurol.*, Paris, 1922, xxxviii. 747.\*
11. Christiansen, V., *ibid.*, 1922, xxxviii. 1169.\*
12. Cohn, T., *Neurol. Centralb.*, Leipzig, 1913, xxxii. 779.
13. Epler, B. L., *Journ. Mich. State Med. Soc.*, Grand Rapids, 1918, xvii. 356.
14. Feer, E., *Jahr. f. Kinderheilk.*, Berlin, 1915, lxxxii. 1.\*
15. Feer, E., *Schweiz. Med. Woch.*, Basel, 1922, iii. 178.
16. Frank, E. S., *Zeitsch. f. Kinderheilk.*, Berlin, 1923, xxxvi. 229.
17. Gerhartz, H., *Münch. med. Woch.*, 1916, lxiii. i. 823.
18. Gerstmann, J., *Wien. klin. Woch.*, 1916, xxix. 1209.
19. Hartenberg, *Presse méd.*, Paris, 1923, xxxii. ii. 776.
20. Herrman, C., *Arch. Intern. Med.*, Chicago, 1916, xvii. 516.\*
21. Hertz, A. F., and Johnson, W., *Proc. Roy. Soc. Med.*, 1912-13 (Clin. Sect.), vi. i. 92.\*
22. Hertz, A. F., and Johnson, W., *ibid.*, 1913-14, vii. i. 11.
23. Holländer, E., *Münch. med. Woch.*, 1910, lvii. ii. 1794.
24. Holländer, E., *Zeitsch. f. d. ges. Neurol. u. Psych.*, Berlin, 1911, Orig., v. 633.
25. Husler, J., *Zeitsch. f. Kinderheilk.*, Berlin, 1914, Orig., x. 116.
26. Irving, G. R., *Med. Press*, Lond., 1922, clxiv. 70.
27. Izawa, Y., *Amer. Journ. Med. Science*, 1923, N. S., clxvi. 185.
28. Janson, G., *Hygiea*, Stockholm, 1921, lxxxiii. 329; *Abstr. in Journ. Amer. Med. Assoc.*, 1921, lxxvii. 502.



29. Jolowicz, E., *Neurol. Centralb.*, Leipzig, 1915, xxxiv. 930.\*
30. Klien, H., *Munch. med. Woch.*, 1921, lxviii. 206.
31. Kraus, W. M., *Rev. neurol.*, Paris, 1921, xxxvii. 357.\*
32. Laignel-Lavastine and Viard, *Nouv. Iconog. d. l. Salpêtr.*, Paris, 1912, xxv. 473.\*
33. Langmead, F., *Proc. Roy. Soc. Med.*, Lond., 1920 (Sect. Dis. Child.), xiii. 6.
34. Leipholdt, C. L., *Med. Journ. S. Africa*, Johannesburg, 1921, xv. 161. (Quoted by Smith.)
35. Lewandowsky, M., *Neurol. Centralb.*, Leipzig, 1913, xxxii. 866.
36. Luce, H., *Deutsch. Zeitsch. f. Nervenheilk.*, Leipzig, 1922, lxxv. 356.
37. Meyer, O. B., *ibid.*, Leipzig, 1922, lxxiv. 204.\*
38. Mirallié, C., et Fortineau, G., *Rev. neurol.*, Paris, 1921, xxxvii. 847.
39. Neel, A. V., *Hosp. Tid.*, Copenhagen, 1916, 5 R., viii. 1253.
40. Pic, A., et Gardère, C., *Lyon méd.*, 1909, cxiii. 61.
41. Reuben, M. S., and Zamkin, H. O., *Arch. of Pediat.*, N. York, 1922, xxxix. 112.\*
42. Schwenke, J., *Deutsch. med. Woch.*, 1922, xlviii. 292.
43. Shaw, H. Batty, *Trans. Clin. Soc.*, Lond., 1905, xxxviii. 222.
44. Simons, A., *Zeitschr. f. d. ges. Neurol. u. Psych.*, Berlin, 1911, Orig., v. 29.\*
45. Simons, A., *ibid.*, Berlin, 1913, Orig., xix. 377.\*
46. Smith, H. L., *Bull. Johns Hopkins Hosp.*, Baltimore, 1921, xxxii. 344.\*
47. Spear, I. J., *Arch. Intern. Med.*, Chicago, 1918, xxi. 39.\*
48. Strauch, A., *Journ. Amer. Med. Assoc.*, Chicago, 1922, lxxviii. 1037.\*
49. Trümner, *Deutsch. med. Woch.*, 1923, xlix. 238.
50. Weber, F. Parkes, *Proc. Roy. Soc. Med.*, Lond., 1912-13 (Neurol. Sect.), vi. ii. 127.
51. Weber, F. Parkes, *Quart. Journ. Med.*, Oxford, 1916-17, x. 131.
52. Weber, F. Parkes, *Proc. Roy. Soc. Med.*, Lond., 1917 (Sect. Dis. Child.), x. i. 117;\* *Clin. Journ.*, 1918, xlvii. 87.\*
53. Weber, F. Parkes, *Med. Press*, Lond., 1924, clxviii. 499.
54. Weber, F. Parkes, and Gunewardene, T. H., *Proc. Roy. Soc. Med.*, Lond., 1918-19 (Sect. Dis. Child.), xii. 13\*; *Ibid.*, Lond., 1920, xiii. 1.
55. Wieland, E., *Schweiz. med. Woch.*, Basel, 1922, iii. 293.

The papers marked with \* contain illustrations.

#### DESCRIPTION OF PLATES.

PLATE 8, FIGS. 1 and 2. Clinical aspect of Case I.

PLATE 9, FIG. 3. Appearance of face, Case II.

FIG. 4. Appearance of face, Case III.

FIG. 5. Appearance of lower limbs and buttocks, Case III.



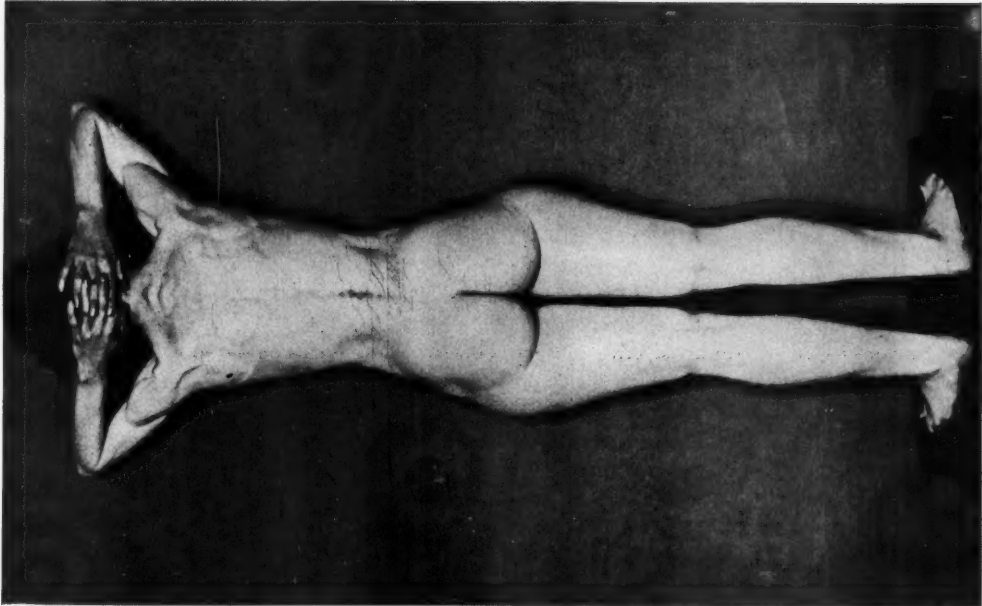


Fig. 2

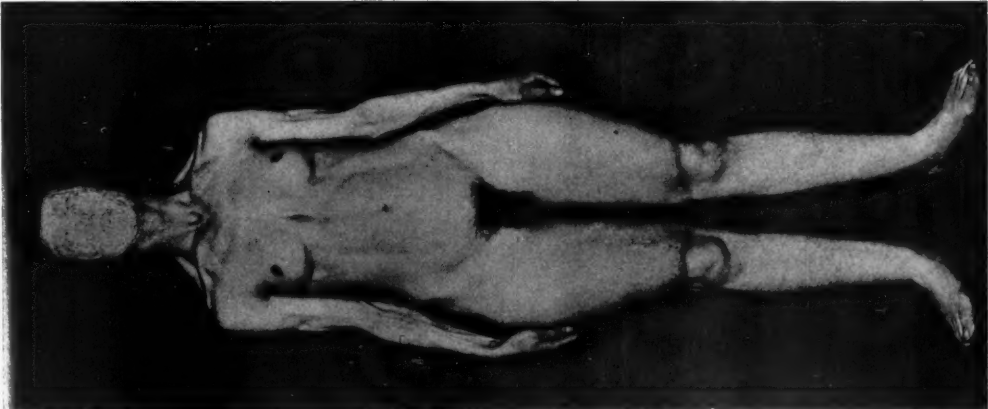


Fig. 1





FIG. 3



FIG. 4

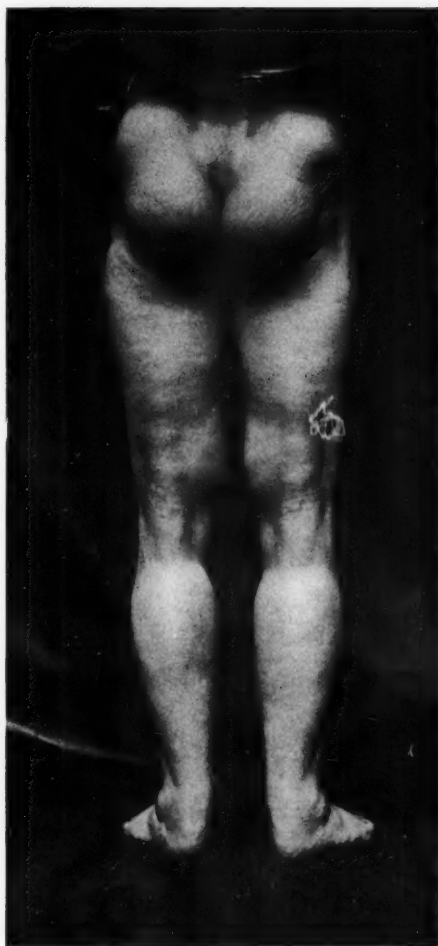
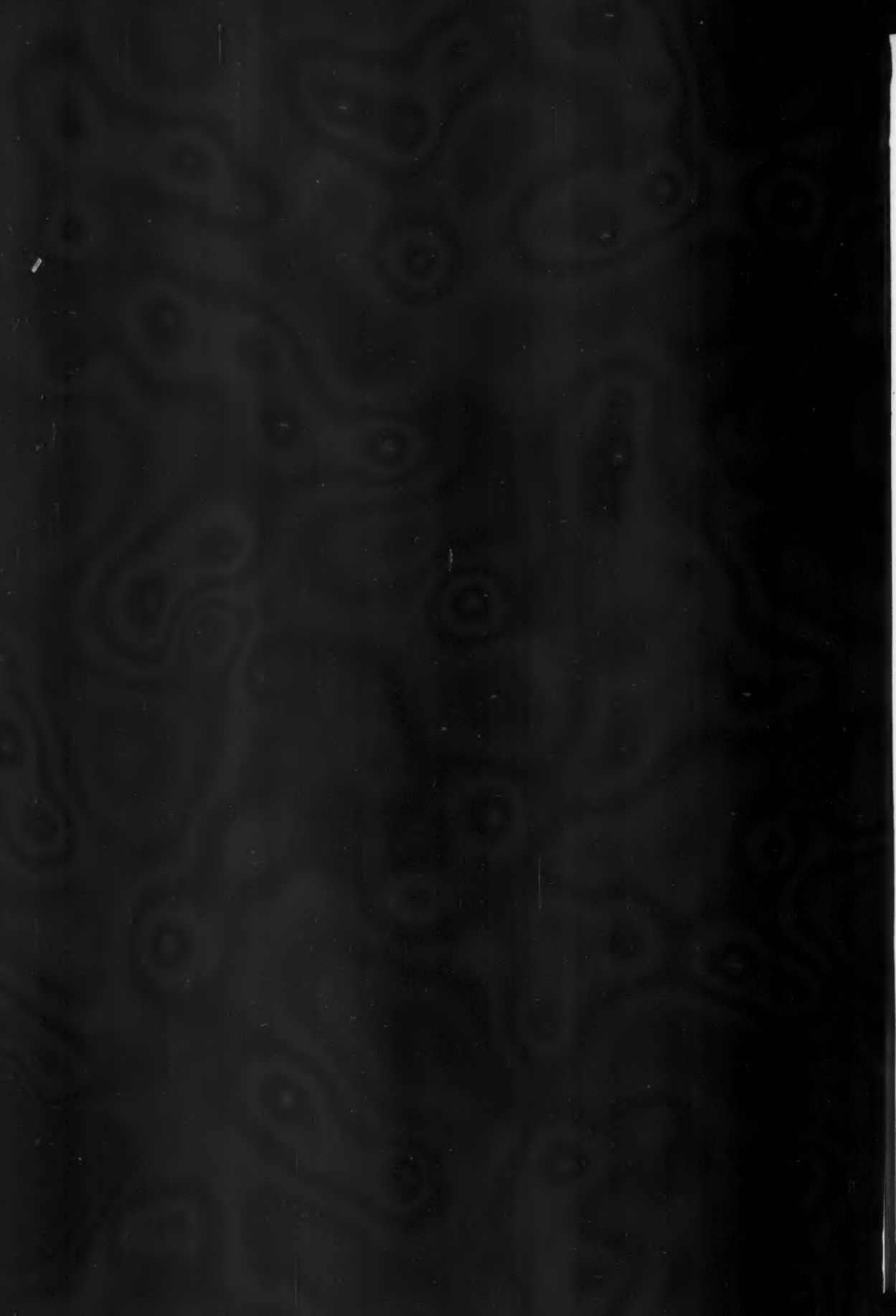


FIG. 5





## THE BLOOD-UREA AND ITS ESTIMATION IN DIABETES MELLITUS<sup>1</sup>

By CHARLES E. BRUNTON

THE object of this investigation was to obtain data as regards the concentration of blood-urea absolutely and relatively to that of blood-sugar in diabetic patients under treatment by insulin, and the relation between the amounts of these two blood constituents. A discussion of the method employed for the estimation of urea is included.

Myers (1921) states that the blood-sugar and blood-urea are increased concurrently under two conditions: (1) In diabetes the blood-urea may be relatively high, and (2) in severe nephritis with a high blood-urea there may be both a high blood-sugar and a 'diabetic curve of sugar tolerance'. The question then arose whether chronic diabetes would give rise to such changes in metabolism that urea excretion would be altered. Dr. Langdon Brown (1921) suggested such a possibility, and quoted both a case of his own which seemed to support the theory and the experience of Dr. Mackenzie Wallis that diabetics in India frequently die of uraemia rather than of diabetic coma. At the time of writing, too, the nature of insulin was uncertain, and it seemed possible that its administration might affect the metabolism of urea either directly or through the kidneys.

A few words must be said about factors which alter the amount of urea in the blood. Those which increase the amount of urea include the ingestion of a diet rich in proteins, numerous conditions which prevent the excretion of urea, such as acute nephritis, terminal nephritis, mercury bichloride or lead poisoning, the poisons of intestinal obstruction or syphilis, and double polycystic kidney, besides certain conditions where the mode of action is doubtful: e.g. malignant diseases, cardio-renal cases. In pneumonia the apparent increase is due to concentration of the blood following effusion of the plasma into the lung alveoli.

Myers (1921) suggests that the rise of blood-urea, found in the blood of diabetics, is due partly to their high protein diet and partly to a complicating nephritis. Naturally a moderate protein diet will act as a protein-rich diet if the patient's kidneys are damaged. Most of the patients whom the writer has investigated were taking a diet which contained about 60 gm. of protein in

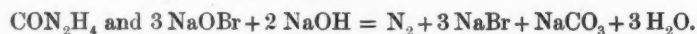
<sup>1</sup> Received August 19, 1924.

twenty-four hours, so that if the diet only were considered their blood-urea might be expected to be lower than normal.

*The Blood-urea in Diabetes Mellitus.*

The blood-sugars were estimated as glucose by Mackenzie Wallis and Gallagher's (1920) modification of the Folin-Wu technique, except that the blood was measured in a previously calibrated pipette instead of on the torsion balance. The method has been checked in many ways and found satisfactory.

Methods for the estimation of urea in solutions may be divided primarily into two classes. A urea compound may be formed as in the xanthidrol method of Fosse (1914), or the urea may be decomposed and one of the products estimated. In the hypobromite method the volume of nitrogen evolved is estimated in accordance with the equation:



This method is inaccurate even with simple solutions of urea and is quite untrustworthy for the estimation of small quantities of urea in organic fluids (Werner, 1923). The volume of gases evolved is influenced by sugar and other substances which may occur in blood or urine. With 5 c.c. of blood it can be used as a rough clinical estimate. Folin, indeed (1905), decomposed urea in an autoclave at 150° C., but his method required several cubic centimetres of blood (1913) and was superseded for ordinary use by the urease methods of Marshall (1914) and of Van Slyke and Cullen (1914), in which the urea is decomposed. Ammonia is next set free from its compounds by the addition of alkali, and is removed from the interfering substances of the blood either by aspiration (with or without heat) or by distillation into a known quantity of standard acid which is then titrated. Folin (1914) distilled into acid the ammonia obtained from the action of urease on his protein-free blood filtrate and then nesslerized the fluid and estimated the colour against a standard of ammonium chloride.

He studied the question of interfering substances and found that direct nesslerization of a blood filtrate tended to be unsatisfactory owing to contamination with proteoses and peptones. In this case the colour of the nesslerized solution becomes greenish instead of pure brown (Folin and Wu, 1919). As such a method was adopted in the present investigation the writer must say at once that, among 250 blood-urea estimations, this phenomenon only occurred in six cases, and in these the blood had been kept (in the ice-chest) for over forty-eight hours. The writer has not tried the xanthidrol method, but has used Van Slyke and Cullen's method, as modified by Fearon (1922), and considers that a choice between them depends on the following factors: Interruptions during work make the Folin distillation method impossible, the expense of a colorimeter and the quality of British daylight is in favour of titration methods, whereas the want of a good water-supply or air-line for aspiration,

and perhaps the slightly longer time which the estimation requires, are in favour of a colorimetric method. The writer thinks that a Kober colorimeter and pent-house containing a 'daylight' electric lamp would decide him in favour of a colorimetric method, but the standard must be matched with itself before estimations are begun, as with artificial light alterations of the colorimeter reflectors are greatly magnified.

Given a well-pointed burette tip, the titration method is as accurate as the colorimetric, but at least 1 c.c. of blood is used instead of the 0.2 c.c. which may be obtained without venepuncture. The method of Twort and Archer (1923), as used by the writer, was as follows: 0.2 c.c. of blood was measured in a pipette which had previously been calibrated with distilled water and blood by weighing on a torsion balance. The blood was blown out into 3 c.c. of twice-boiled distilled water. Urease solution 0.2 c.c. (made by freshly dissolving a urease Dunning tablet in 10 c.c. of twice-boiled water) was added and the tube incubated in a water-bath at 45–50° C.; the bath being allowed to cool gradually and usually reaching 20–30° C. in half an hour. After incubation 0.3 c.c. of a 10 per cent. sodium tungstate solution in water and 0.3 c.c. of a 2N/3 solution of  $\text{H}_2\text{SO}_4$  were added, the tube being rolled in the hand during the addition of the latter. The total volume was then made up to 8 c.c. with water and the precipitate was removed, at first by filtration, but later with absolute completeness and ease by a centrifuge. Exactly 5 c.c. of the filtrate or crystal clear supernatant fluid were pipetted into 5 c.c. of water and 2 c.c. of Nessler's solution were added. The Nessler's solution was made up very carefully from pure  $\text{HgI}_2$  according to Folin's first directions (1919), except that the solution of  $\text{NaOH}$  was allowed to stand forty-eight hours before being filtered. After a few hours this solution became constant, and trouble only once occurred with cloudiness in a single specimen whose duplicate tube gave no trouble. Such trouble as that of which Stanford (1923) complains was never experienced though our solution contained, after nesslerization, over 72 'c.mg.' N. Dr. Archer believes that turbidity in urea estimations is due to excess urease, and chose his quantity accordingly. These mixtures remained clear for at least an hour and the standards were sometimes unchanged forty-eight hours after being made up. The Nessler's solution keeps for at least six months in the dark. The standard with which the nesslerized filtrate was compared contained an amount of  $(\text{NH}_4)_2\text{SO}_4$  equal to 0.0001 gm. of urea in 1 c.c. This was diluted with water to 10 c.c. when required. The whole operation took fifty minutes, of which thirty were due to the time of incubation, when the work required no attention whatever (whereas aspiration with a water-pump needs to be watched rather carefully). If six specimens were to be estimated the whole work usually took about  $1\frac{1}{4}$  to  $1\frac{1}{2}$  hours when very accurate colorimeter readings were desired. For clinical work only thirty minutes would be needed. As has been said, duplicate estimations of the blood-urea were usually done. The following are ten consecutive results where routine duplicate readings were done. The amounts are in mg. urea per 100 c.c. of blood:

1.	24.1	23.0	6.	35.6	35.5
2.	52.2	53.3	7.	65.6	64.5
3.	38.1	39.7	8.	100.3	101.6
4.	35.1	38.2	9.	30.2	30.2
5.	27.5	28.3	10.	27.0	27.1

The following experiment was done to test the method, and a sample of urea (twice crystallized) supplied by the British Drug Houses, with a melting-point of  $132^{\circ}\text{C}$ ., ash nil and sulphate absent. Known amounts of it were added to sheep's blood of known urea content, and to a patient's blood.

The results were as follows :

	mg. %	Average.	Theoret.	% Error.
Urea value of sheep's blood	37.9	37.85	—	—
" " " " blood-urea = 31.3 mg. %	37.8			
" " " " " =	69.8	69.20	69.15	0.09
" " " " " = 62.6 mg. %	68.6			
" " " " " =	106.2	107.2	100.45	6.8
" " " " " =	108.2			
Patient's blood (average of two readings)	24.2	—	—	—
Blood and urea equal to 31.3 mg. % (average of two readings)	54.7	—	55.5	1.5

Blank experiments with reagents alone were unsatisfactory, as the small opalescent particles of the urease solutions were badly precipitated in the absence of blood, and produced a high reading when nesslerization was done, whether removal was attempted by centrifuge or filtering repeatedly. The lowest reading obtained for blank reagents was equal to 1.4 mg. urea per cent., and after consultation with Dr. Archer the writer decided to subtract 4 mg. per cent. from all his gross urea results. Separate pipettes were kept for each reagent. The test-tubes used for preparing the nesslerized mixture were washed with  $\text{HNO}_3$  and then with three changes of boiled water after each experiment: this removes residue and may partly explain why cloudiness never appeared on nesslerizing. The same tubes were always used and were numbered so that any individual peculiarity might be checked: none was found. It was noted that if the  $\text{H}_2\text{SO}_4$  reagent was not kept carefully corked it absorbed ammonia. Filter-papers, too, have been found to absorb considerable amounts of ammonia, as may be seen on soaking one in 10 c.c. of water and nesslerizing. For this reason the removal of the protein precipitate by centrifuge was preferred. Urease solution made up from urease Dunning tablets does not keep for twenty-four hours. A fresh solution of urea (theoretical 0.10 mg. urea) was estimated and a result of 0.091 obtained. The following day the same solution, with urease solution twenty-four hours old and kept corked at  $12^{\circ}\text{C}$ ., gave values of 0.063 and 0.067 mg.—about 36 per cent. lower. As far as the writer is aware this fact has not previously been noted.

To see whether the estimation could be stopped at various points, blood was estimated at once and after standing for twenty-four hours in an ice-chest. Similar results were always obtained. The method was also stopped after incubation: the blood-tube was capped and was kept at  $18-19^{\circ}\text{C}$ . for twenty-one hours. Urea value estimated at once = 13.6 mg. per cent.; estimated after

twenty-one hours = 14.2 mg. per cent. If the filtrate stood for eighteen hours mixed with water previous to the final nesslerization no change of value took place. The oxalate used for collecting the blood gave no colour with Nessler's solution. To test the time required for incubation, tubes were incubated for fifteen minutes and thirty minutes at 40-50° C. The results were respectively 36 mg. and 39.7 mg. urea per cent. On further incubation for ninety minutes no increases occurred.

The method is excellent if the reagents are carefully made up and vessels kept clean. It is very simple to carry out, the reagents do not deteriorate rapidly, and work can be interrupted for a few minutes at almost any point or for a few hours at several points without injury to the results.

The method of estimation used for urea did not distinguish blood-urea and blood-ammonia. Attempts to find a urease in human tissues has failed, nor would life be possible if the alkalinity of the blood was much raised by free  $\text{NH}_3$ -ions (Carnot et Gerard (1919)). Nash and Benedict (1921) present strong evidence to show that urinary ammonia is produced wholly in the kidneys, so that the amount normally circulating in the body is very small unless in extensive liver deficiency. These authors found 0.06 to 0.12 mg. of ammonia-N per 100 c.c. in the carotid blood in dogs, and amounts varying from 0.0 to 1 mg. of ammonia-N have been found by different observers in human blood. Nash and Benedict show that the estimated amount in whole blood increases on the blood standing for half an hour, even when on ice, and that this increase is greater if the blood is kept at room temperature. The change is almost sufficient to explain the amounts of blood ammonia usually found, and as Myers (1921) has already stated, 'the existence of appreciable amounts of ammonia in human blood is doubtful'. Nevertheless it is regretted that circumstances prevented the careful estimation of blood ammonia in the cases of coma examined (Case 13).

### *Results.*

With regard to blood-urea the following questions were considered: (1) Does any relation exist between the absolute amount of sugar and of urea found in the blood of diabetic patients who are being treated with insulin? (2) Does the administration of insulin produce any alteration in the amount of blood-urea as compared with the amount in diabetics whose blood-sugar can be kept normal by restriction of diet and without insulin. (3) Does the duration of diabetes mellitus influence the amount of blood-urea?

The results given in Table I furnish an answer to the first of these questions. They show the concentrations of (1) sugar and (2) urea in the blood, and (3) the diet protein of 25 diabetic patients arranged according to the blood-sugar concentration. The carbohydrate equilibrium of these patients was in some cases maintained by diet restrictions alone, while in others a dose of insulin varying from 5 to 120 Toronto units was given during twenty-four hours.

The insulin used was either the A B brand (British Drug Houses, Ltd.) or that



supplied by Burroughs, Wellcome & Co. The time of its administration is given in the table, as is also the interval between the last meal and the taking of the blood sample. The blood was usually obtained from the finger, but in the case of patients whose circulation while in bed was poor it was obtained by venepuncture.

Those patients who are described in the table as having a daily protein intake of 60 gm. were also receiving about 10 gm. of carbohydrate and 36 gm. of fat per day.

TABLE I.

No.	Blood-sugar, Mg. in 100 c.c.	Insulin.			Urea, Mg. in 100 c.c.	Diet Protein.		
		Last Dose, in Units.	Time since, in hrs.	Daily Units.		Grm. Last Meal.	Time since Meal.	Daily gm.
A. 1	22	—	nil	—	24.5	15	2½	43
2	95	—	"	—	25.5	14	2½	61
3	115	—	"	—	17.0	Hospital diet, no diabetes		
4	137	—	"	—	26.0	15	2½	24
5	173	—	"	—	29.9	Alimentary rest		
B. 1	88	5	24	5	25.0	15	1	60
2	90	5	3	5	25.6	15	2½	60
3	108	15	15	45	20.2	5	1	40
4	108	16	2½	16	24.5	—	2½	—
5	115	15	17½	45	30.8	13	1	57
6	137	10	24	10	31.5	4.5	2½	24
7	137	10	24	10	48.7	*10	2	60
8	140	10	24	10	34.8	*10	2	60
9	207	10	15	25	23.5	15	1	60
10	218	10	5	20	35.0	*12	2	60
11	242	10	24	10	28.0	*10	2	60
12	250	10	14	40	41.4	Alimentary rest		
13	250	16	24	16	51.8	15	1	60
14	266	15	24	15	14.6	15	1	60
15	266	15	24	15	28.3	15	1	60
16	268	10	4	90	44.7	Alimentary rest		
17	300	20	5	110	30.9	4.5	1	24
18	336	20	24	20	34.7	*12	3	60
19	466	—	nil	—	84.2	Alimentary rest		
20	620	—	"	—	27.0	" "		

\* Out-patients on weighed diet: amounts approximate.

As regards the excretory power of their kidneys, all the patients studied passed a urine free from protein, had blood-pressure well within the normal limits, and there was no suspicion of nephritis either in their history or in their physical signs. In the case of the three patients who showed abnormally high blood-urea it was unfortunately impossible to do a urea concentration test. In only one case was a low blood-urea content found: No. B 14. This remains unexplained, as on other occasions this patient's urea figure was normal on a similar diet containing 60 gm. of protein in each twenty-four hours. The estimation was repeated four times, and the reagents used gave almost theoretical results when known amounts of urea were added to samples of the patient's blood and the differences were estimated. In this case none of the following hypotheses were admissible: unusually low protein diet, a permanently low renal threshold for urea, pregnancy, or the breaking down of the urea in the



circulating blood. The patient, however, on the evening of the following day, felt ill for an hour shortly after her evening dose of insulin; the blood-sugar on the same day, taken one hour after insulin, was 0.118 per cent.; so that some connexion suggests itself between a low blood-urea and hypoglycaemia. The case may be compared with Case 13, i.e. a case of diabetic coma in Table III.

The results shown in Table I warrant the conclusion that in diabetes, whether treated with or without insulin, no relationship can be found between the blood-sugar and blood-urea. A connexion was suggested in B 13 and 14, to which reference has been made, as well as in B 16, 17, and 19, where both the blood-urea and blood-sugar fell after the administration of insulin, but in another case of coma (B 12, 20) the blood-urea rose as the blood-sugar decreased. These two cases are quoted again in Table III as Case 13.

#### *Insulin and Blood-urea.*

The question as to whether insulin causes any alteration in the blood-urea content is answered in the negative by the results given in Table I. To confirm this conclusion four blood-urea and blood-sugar readings were made and compared immediately before, and two and a half hours after, dinner.

The results are given in Table II.

TABLE II.

Insulin.	Dinner.		Fat.	Blood-sugar before: grm. in 100 c.c.	Blood-urea before: mg. in 100 c.c.	Blood-sugar after: grm. in 100 c.c.	Blood-urea after: mg. in 100 c.c.
	Carbo- hydrate.	Grm. Pro- tein.					
None	13.5	14	30	0.098	28.1	0.095	25.5
None	13.5	14	30	0.082	26.2	0.078	25.7
None	2.0	5	3	0.137	26.2	0.134	24.0
5 units 3 hrs. before	11.0	12	28	0.090	25.6	0.115	24.4

Insulin, therefore, does not cause any alteration in the blood-urea.

Table III shows the duration of the diabetes and the blood-urea as estimated on one or more dates. In all cases which are included, the duration since the first-noticed symptom of disease was definitely known: it varied from three months to seventeen years. For almost all the time mentioned, patients had been under treatment either continuously or at intervals. The sex, age, and corresponding blood-sugars are shown. Apart from the blood-urea of Cases 13 and 14 when admitted in coma, the highest readings are in Cases 9 and 11, of three and four years' duration respectively. Case 11 also gave one of the lowest readings on another date under conditions which were almost similar as regards blood-sugar, while the diet and dose of insulin were the same on each date. Case 13, with a duration of six years, had a urea of 30.9 mg. per 100 c.c. on a diet containing 40 grm. of protein per twenty-four hours, and Case 4, aged 66, with a duration of seventeen years, a diet containing 60 grm. of protein per day,

a blood-pressure of 160 mm. Hg., and no proteinuria, had a blood-urea of only 25.6 mg. per 100 c.c.

Cases 13 and 14 show very different concentrations of blood-urea following the exhibition of insulin in cases of diabetic coma. The writer considers the question worthy of further study, but the results, which were carefully checked, show at least that diabetic coma is not necessarily accompanied by a high blood-urea concentration. Indeed coma and the acidosis of nephritis are now being attributed to the retention of phosphates (Marriott and Howland (1918), de Wesselow (1923)), and urea seems likely to be acquitted of the charge.

TABLE III.

Case.	Sex.	Age (years).	Duration (years).	Date.	Blood-sugar. Grm. per 100 c.c.	Blood-urea. Mg. per 100 c.c.
1	M.	27	$\frac{1}{2}$	3.11.23	0.098	28.1
				7.11.23	0.082	24.5
2	M.	28	$\frac{1}{4}$	30.10.23	0.088	25.0
3	M.	40	2	31.10.23	0.137	31.5
4	M.	63	17	3.11.23	0.113	25.6
5	F.	16	2	14.11.23	0.207	23.5
				19.12.23	0.115	30.8
6	M.	66	$\frac{1}{4}$	9. 2.23	0.173	29.9
7	F.	23	1 $\frac{1}{2}$	22.11.23	0.336	34.7
8	F.	43	2 $\frac{1}{2}$	11.11.23	0.137	31.5
				3.12.23	0.266	28.3
9	M.	46	3	2.11.23	0.138	48.7
				15.11.23	0.140	34.8
				20.12.23	0.168	45.3
10	F.	52	3 $\frac{1}{2}$	15.11.23	0.242	28.0
11	F.	20	4	17.11.23	0.250	41.4
				3.12.23	0.266	14.6
12	F.	20	1	13.12.23	0.108	24.5
13	F.	56	6	23.11.23	0.466	82.2
				24.11.23	0.268	44.7
				27.11.23	0.300	30.9
				19.12.23	0.168	24.1
				5.1.24	0.215	21.9
14	F.	20	$\frac{1}{4}$	4.1.24	0.620	27.0
				5.1.24	0.250	41.4

It seems certain that the duration of diabetes does not bear any relation to the blood-urea content. Diabetes mellitus cannot be said necessarily to lessen the kidneys' excretory power for urea. That power is not always lost in diabetic coma.

#### *Summary.*

1. Twort and Archer's method for the estimation of blood-urea has been investigated and found to be very satisfactory.
2. No relation exists between the amounts of blood-sugar and of blood-urea in patients suffering from diabetes mellitus.
3. The administration of insulin has not been proved to alter the concentration of blood-urea.
4. The duration of diabetes mellitus does not necessarily increase the concentration of blood-urea.

5. Diabetic coma is not necessarily accompanied by an abnormal blood-urea concentration.

The writer wishes to express his indebtedness to Sir Frederick Andrewes, F.R.S., Director of the Pathological Department, St. Bartholomew's Hospital, for kindly placing laboratory facilities at his disposal.

He would also wish to acknowledge his gratitude to members of the Staff at St. Bartholomew's Hospital for kindly allowing him access to patients; and his deep appreciation of the kindness and help which he has received from Dr. Mackenzie Wallis, Chemical Pathologist to the Hospital, and from Dr. H. E. Archer, his assistant.

He returns sincere thanks to the British Medical Association for a grant towards the expenses of the work.

#### REFERENCES.

- Brown, Langdon, *Proc. Roy. Soc. Med.*, Lond., 1921-22 (Sect. Ther. and Pharm.), xv. 3. 1.  
 de Wesselow, *Quart. Journ. Med.*, Oxford, 1922-23, xvi. 341.  
 Fearon, private communication, 1922.  
 Folin, *Amer. Journ. Physiol.*, Boston, 1905, xiii. 45, 66, 117.  
 Folin, *Journ. Biol. Chem.*, Baltimore, 1913, xiii. 469, xiv. 29.  
 Folin, *ibid.*, Baltimore, 1914, xvii. 475.  
 Folin and Wu, *ibid.*, Baltimore, 1919, xxxviii. 81.  
 Fosse, *Comptes rendus*, Paris, 1914, clviii. 1076.  
 Marriott and Howland, *Arch. Int. Med.*, Chicago, 1918, xxii. 477.  
 Marshall, *Journ. Biol. Chem.*, Baltimore, 1914, xvii. 351.  
 Myers, *Pract. Chem. Anal. of Blood*, Lond., 1921.  
 Nash and Benedict, *Journ. Biol. Chem.*, Baltimore, 1921, xlviii. 463.  
 Stanford, *Biochem. Journ.*, Camb., 1923, xvii. 844.  
 Twort and Archer, *Lancet*, Lond., 1923, i. 1102.  
 Van Slyke and Cullen, *Journ. Biol. Chem.*, Baltimore, 1914, xix. 141.  
 Wallis and Gallagher, *Lancet*, Lond., 1920, ii. 784.  
 Werner, *The Chemistry of Urea*, Lond., 1923.

## LYMPHOBLASTIC ERYTHRODERMIA<sup>1</sup>

By JAMES H. SEQUEIRA AND PHILIP N. PANTON

With Plates 10 and 11

IN December 1921 we published in the *British Journal of Dermatology and Syphilis* (1) an account of three cases of a peculiar skin affection characterized by (a) erythrodermia, and (b) a specific change in the blood.

By the courtesy of Dr. Robert Hutchison we have had the opportunity of studying another case of this type in which an autopsy was obtained, and deem the condition of sufficient interest to the general physician to warrant this communication.

The name 'erythrodermia' is applied by dermatologists to affections characterized by a persistent and universal redness of the skin. The whole integument from the crown of the head to the tips of the fingers and toes is involved. In some of the erythrodermias an extensive desquamation is a characteristic feature. It occurs, for example, in pityriasis rubra, and in general exfoliative dermatitis, but there is a type in which the whole skin becomes red without excessive scaling. To a patient suffering from this type of erythrodermia the name 'homme rouge' has long been applied in the French clinics. Characteristic examples of this condition are sometimes seen in the premycotic stage of mycosis (granuloma) fungoides.

In 1915 a case of erythrodermia with a peculiar blood-picture came under our observation, and was shown at the Dermatological Section of the Royal Society of Medicine, and the following is a brief summary of the history of this and four other cases:

*Case I.* William B., aged 60 years, was admitted to the London Hospital on October 1, 1915. There was nothing of importance in the family history. In 1913 he discovered a 'red patch' on his shoulders and the eruption gradually spread until the whole surface was affected. On admission the patient was a characteristic 'homme rouge', the skin everywhere being of a brick-red colour; the surface was smooth except on the lower extremities, where there was slight scaling and oedema. The eruption itched intensely. The lymphatic glands in the neck, axillae, and groins were enlarged and movable but painless, and not tender. Radiographic examination failed to show glandular enlargement in the thorax. The liver and spleen were not enlarged. The urine was normal. The patient was under observation in and out of hospital until 1919. No material change took place in the skin, but the hair of the scalp and eyebrows dis-

<sup>1</sup> Received September 1, 1924.

appeared, while that of the face, axillary, and pubic regions became scanty. There was no pyrexia during the several periods when the patient was in hospital. In 1919 the mental condition became abnormal, the patient being very depressed, constantly scratching himself, and frequently passing urine and faeces in bed. The loss of control was such as is met with in dementia. There was never any loss of consciousness. The mental state rapidly deteriorated and the patient was ultimately removed to his home and died. There was no autopsy. The Wassermann reaction was made several times and was always negative. The blood was examined on numerous occasions, and three characteristic counts at intervals were as follows:

	Oct. 5, 1915.	April 12, 1919.	May 5, 1919.
Red cells	4,500,000	3,999,000	4,650,000
Haemoglobin	—	70 %	55 %
Leucocytes	8,000	32,000	16,000
	%	%	%
Polynuclear neutrophils	38.0	16.5	35.5
" eosinophils	1.0	6.5	3.0
Small lymphocytes	42.0	75.0	59.5
Large lymphocytes	13.5	—	—
Large hyaline cells	2.0	2.0	2.0
Coarsely granular basophils	0.5	—	—
Neutrophil myelocytes	1.0	—	—
Myeloblasts	2.0	—	—
	100.0	100.0	100.0

The change in the blood condition found on May 5, 1919, followed intravenous injections of arsenic (novarsenobillon). A cervical gland was removed for examination in 1919, and Professor Turnbull reported that he was unable to detect evidence of lymphadenoid leukaemia. A portion of skin was also examined and showed chronic inflammatory changes, but there was nothing suggestive of mycosis fungoides.

*Case II.* James S., aged 40 years, a groom-gardener, was admitted to the London Hospital under the care of Dr. Sequeira on May 3, 1921. He was born in Devonshire and was unmarried. The family history was unimportant. The patient had measles and pertussis in infancy, and 'rheumatism' in 1909. There was no history or evidence of syphilis.

In January 1919 he was in the Remount Department at Salonika, when the skin of the hands and feet became dry and easily cracked and his face 'peeled'. He was treated as a case of eczema and returned home in May 1919, but was no better. He was obliged to give up his work in July 1920 owing to dryness, stiffness, and hardness of the skin, with general 'peeling'. In November 1920 he noticed the skin had become dark.

On admission there was a general erythrodermia with slight exfoliation. The scaling ceased with the application of unguentum plumbi subacetatis. The skin everywhere was of a brick-red colour and felt thick on palpation. Sweating was free. There was much itching, but no tenderness, and the skin was supple. The nails were normal. There was no evidence of venereal disease. The inguinal glands were slightly enlarged. There was no apparent increase in the size of the cervical and axillary glands. The eyes were slightly prominent with a little epiphora. The thyroid was not enlarged. The Wassermann reaction was negative. There were no changes in the cerebro-spinal fluid.

Numerous examinations of the blood were made. The red cells ranged from 5,500,000 to 4,300,000, the haemoglobin from 90 per cent. to 85 per cent.; the colour index from 0.9 to 0.8. Leucocytes from an average of seven counts

were 20,794, the highest being 30,800, and the lowest 13,680. The conditions found in the stained blood had exactly the features found in Case I:

	May 6, 1921.	May 11, 1921.	May 18, 1921.	May 25, 1921.
	%	%	%	%
Polynuclear neutrophils	26.0	22.0	25.0	24.6
" eosinophils	3.5	2.5	3.0	1.4
Small lymphocytes	66.5	70.0	65.5	70.0
Large lymphocytes	1.0	3.0	1.5	1.2
Large hyaline cells	3.0	2.0	5.0	2.4
Coarsely granular basophils	—	0.5	—	0.4
	100.0	100.0	100.0	100.0

	June 1, 1921.	June 9, 1921.	June 15, 1921.
	%	%	%
Polynuclear neutrophils	18.4	34.0	25.5
" eosinophils	1.6	3.0	2.0
Small lymphocytes	76.6	59.0	68.5
Large lymphocytes	0.8	0.5	0.5
Large hyaline cells	2.6	3.5	3.0
Coarsely granular basophils	—	—	0.5
	100.0	100.0	100.0

Professor Turnbull examined a portion of the skin, and reported that there was a slight keratosis of the epidermis, with conspicuous hypertrophy of the Malpighian layer, in which there were a few karyokineses. The cells of the Malpighian layer, especially the basal cells, showed perinuclear vacuolation.

In the dermis there was considerable infiltration almost confined to the papillary layer. The majority of the infiltrating cells were spindle and stellate. Many of these contained granules of iron-free pigment. The other cells were lymphocytes and adventitial cells with a few plasma cells. No eosinophils were seen. The vessels were not engorged.

The patient's condition had not materially changed to date. Local applications gave little relief and X-ray treatment was tried without benefit.

The publication of the account of this case led Dr. W. H. Brown, of Glasgow, to send us particulars of his case, which he was good enough to allow us to use, and we append here an abstract:

*Case III.* Mrs. J., aged 64, married late in life, no children. Family and personal history unimportant.

For two years the patient had been troubled with itching of the skin, beginning on the trunk and becoming generalized. Twelve months later the skin began to get red, commencing on the trunk; the redness gradually spread until the whole surface became involved, the face and hands being the parts last affected.

The patient, an obese woman, was found on admission to hospital to be suffering from a generalized erythrodermia. The skin of the face and head suggested a boiled lobster. There was no desquamation. The ears were congested and beginning to weep—the result of scratching. The whole scalp was red, slightly scaly, and infiltrated. The hair was thin. There was some blepharitis. The lips were a little blue. On the chest and back the redness was fairly uniform, but on the abdomen and lumbar regions more scarlatiniform. The redness was less marked on the extremities, and everywhere faded on pressure. Itching was intolerable and practically constant. There was no evidence of venereal disease, and the appetite was good. Slight indicanuria was



observed, but the urine contained neither albumin nor sugar. There was an occasional evening temperature of 99° F. The blood-picture on two observations was:

Red blood cells	4,760,000	3,720,000
White blood cells	27,400	23,000
Haemoglobin	50 %	55 %
	%	%
Polynuclear neutrophils	35.5	29.5
" eosinophils	3.3	3.6
Small lymphocytes	53.0	60.4
Large lymphocytes	4.6	6.0
Large hyaline cells	3.6	0.5

The patient got slightly worse. The intertrigo of the breasts and axillae became very troublesome, and an irritable weeping dermatitis of the ears and scalp developed. Local treatment was found to be useless. X-ray application gave temporary relief. The patient died in great misery two or three weeks after leaving hospital.

*Case IV.* The history of this patient and a plate (Plate 11) illustrating his condition we are able to include in this series by the courtesy of our colleague, Dr. Robert Hutchison, who very kindly supplied us with the plate and gave us the opportunity of examining the patient while he was under his care.

The patient, George S., aged 60, was originally shown at the British Medical Association in Newcastle in June 1921, and by Dr. S. E. Dore at the Royal Society of Medicine in July 1922 (2). Below is an abstract from Dr. Dore's remarks at the demonstration:

'The patient was shown by Dr. Patterson in June 1921, and he then had an eruption on the trunk and limbs quite different from the present appearance; it was much pinker in colour and blue in parts, and was striated and retiform in character. The diagnosis made at that time was parapsoriasis, but Dr. Heath and some other members regarded it as an instance of angioma serpiginosum. The patient has since been in Edinburgh Royal Infirmary under Dr. Cranston Low, from January to March 1922. Dr. Cranston Low kindly wrote to me about him and said he regarded the case as one of parakeratosis variegata of the type described by Radcliffe Crocker as xantho-erythrodermia perstans, and pointed out that the yellow colour became apparent on pressing the blood out of the skin. He had tried sulphur, salicylic acid, tar, and chrysarobin without effect. X-rays and the mercury vapour lamp also failed to influence the eruption. Eight injections of sterilized milk were then administered intramuscularly into the buttocks twice a week, beginning with 2.5 c.c. and increasing to 10 c.c. No rise in temperature followed, but there was a marked leucocytosis for twenty-four hours after the injection, and there seemed to be a slight improvement in the eruption. A piece of skin was excised, but showed nothing unusual. When the patient was seen at St. Thomas's Hospital, in June 1922, he stated that he had become worse during the past eight or ten months and complained of severe itching. The eruption had lost its original distinctive characters and had become merged in a general redness affecting the scalp and face and the upper part of the trunk, leaving only the tips of the elbows, the palms, and the legs free. The skin was of a deep red, almost crimson tint, was distinctly thickened and flaccid, and showed rugosities due to keratosis and scaling, the last feature being especially developed on the front of the chest and upper abdomen, the general appearance being comparable to that of the hide of an elephant. There was also considerable tenderness of the skin on pressure, but this became less noticeable at a later date. On physical examination at the hospital nothing was found except a definite enlargement of the spleen, which could be palpated beneath the costal margin.'

One of us (J. H. S.) saw the patient at the meeting, and was of opinion that the appearance was that of a form of erythrodermia to which we had given the name 'lymphoblastic erythrodermia', but that the essential feature of these cases was the persistently high percentage of the lymphocytes. The blood-count as submitted afterwards by Dr. Dore gave the following figures:

Red cells . . . . .	6,352,000 per c.mm.
White cells . . . . .	8,400 " "
Haemoglobin . . . . .	90 per cent.
Colour index . . . . .	0.9 per cent.

*Differential Count of White Cells.*

	%
Polynuclear neutrophils . . . . .	46.0
" eosinophils . . . . .	—
" basophils . . . . .	—
Small lymphocytes . . . . .	36.0
Large lymphocytes . . . . .	14.0
Large mononuclears . . . . .	3.0
Myelocyte neutrophils . . . . .	1.0

The patient was admitted to the London Hospital under the care of Dr. Robert Hutchinson on May 27, 1923, and by his courtesy we not only had the opportunity of examining him, but are permitted to publish herewith the further history of his case. Abstract of notes:

'May 20, 1923, the patient "caught cold", was feverish, and had several attacks of epistaxis. His ankles became swollen. Three days later he got out of bed and fell, abrading his shoulder, back, and right arm. On May 26 he was slightly delirious, and his relatives noticed that his abdomen was swollen.

'Condition on admission to hospital: A well-nourished man with a purplish discoloration of the skin all over the body, the colour being less marked on the feet and lower thirds of the legs. The skin was rough and scaly and easily abraded. There were no local swellings on the skin, but a certain degree of general infiltration. The visible mucous membranes were not pigmented. The fingers were moderately clubbed. He was then mildly delirious. Temperature 101° F. Respiration 30. Pulse 96, regular, medium beat and tension. The first and second heart sounds were heard in all areas, the pulmonary sound was accentuated. A systolic murmur was heard all over the pericardium, but was most marked at the base.

'Lungs. Percussion not impaired. Breath sounds vesicular. Coarse crepitations posteriorly at the right base.

'Abdomen distended and tympanitic. Spleen palpable three inches below left costal margin. Liver not enlarged. No evidence of free fluid.

'Slight oedema of both ankles.

'Glands. Cervical, axillary, and inguinal glands enlarged and "matted".

'Progress: Delirium subsided. Temperature fell to normal on the seventh day after admission. The patient was generally contented but restless at times, with occasional delirium at night. The urine was normal.

'On the eighth day after admission the temperature rose to 103° F. and the pulse to 120. Bubbling râles were heard at both bases. On occasions the air passages appeared choked with mucus. Two days later the temperature rose to 108° F. and the patient died.

*Blood Examination.*

	May 27, 1923.	June 4, 1923.
Erythrocytes	3,080,000	3,080,000
Haemoglobin	65 %	65 %
Colour index	1.1 %	1.1
Leucocytes	57,200	49,200
	%	%
Polynuclear neutrophils	18.2	40.4
" eosinophils	—	—
Small lymphocytes	80.0	56.4
Large lymphocytes	0.2	0.2
Large hyaline cells	1.6	3.0
	100.0	100.0

'The patient's colour had altered since he was shown by Dr. Dore at the Royal Society of Medicine. The skin was of a more purple tint, and we think may partly be accounted for by the respiratory trouble. The blood count, it will be observed, now had the characteristic lymphocytosis seen in the other cases of this group, and in the year which had elapsed between Dr. Dore's examination and our own the total number of lymphocytes had greatly increased.

'*Post mortem* the skin showed, in addition to the pigmentation, extensive areas of thickening. All portions of skin examined microscopically showed a lymphocytic infiltration of the reticular zone of the dermis. In the portions of thickened skin this infiltration was massive. Iron pigment was present in the reticular zone of the dermis, and was most abundant immediately beneath the infiltrations; in the papillary zone there was pigment which rarely gave the reaction of iron. The spleen showed great enlargement and extensive infarction. Many of the lymph glands were enlarged and showed marked infiltration to the naked eye. The femur contained rich pinkish-grey marrow in the head of the great trochanter, in the neck, and in the upper 10 cm. of the shaft; in the remainder of the femur was a moist, more gelatinous, red marrow. There was a soft homogeneous pink-grey marrow throughout the humerus. The liver was large, firm, and pale, without visible infiltration. It did not give a free iron reaction. Microscopical examination showed infiltration of lymphoid cells in the portal systems. Both kidneys contained anaemic infarcts.'

*Case V.* This was also seen by one of us (J. H. S.) at the Royal Society of Medicine in July 1922, and was exhibited by Dr. William Dyson. The following is an abstract of his remarks on the case:

'The patient, H. M., a male, aged 23, was admitted as an in-patient to the Manchester Hospital for Diseases of the Skin, on June 13, 1922.

'History: In June 1919, whilst in France, an erythematous eruption appeared on the front of the chest. The eruption gradually spread, involving the whole of the trunk, face, and legs. It reached a maximum eighteen months ago, and since that date has remained stationary. When on leave he was isolated in the Grove Military Hospital for (?) German measles, and at the depot at Shrewsbury was under observation for suspected scarlet fever. His general health is good, but he complains of intense pruritus, which is worse when he becomes warm and causes him to have sleepless nights. Appetite good; bowels constipated. In October 1918 he suffered from trench fever. He was invalided out of the army for neurasthenia.

'Family history good, with no history of a similar condition in any of his relatives.

'Condition on admission: Fair, red-headed, freckled, of good physique; has a general erythema, most intense over a band-like area surrounding the body, extending from just below the nipple line to the lower costal margin. Over this

area the skin has the appearance of being slightly swollen and oedematous. In the groins and on the inner side of the upper arms in the region of the axillae the rash is mottled in appearance, and purpuric. There is no desquamation, nor has there been any whilst he has been under my observation. There was marked dermatographia before admission, but this has now disappeared.

'The lymphatic glands, both in the groins and axillae, are distinctly enlarged, equalling the size of a hazel nut. Liver and spleen normal. Heart, lungs, and urine normal. Teeth good. Tonsils not enlarged nor showing evidence of sepsis. Knee-jerks and abdominal reflexes exaggerated.

'The patient is of a nervous temperament.

Blood count (July 5, 1922):

Red blood cells . . . . .	4,800,000 per c.mm.
White blood cells . . . . .	8,800 per c.mm.

*Differential Blood Count:*

Polynuclear neutrophils . . . . .	43 per cent.
Small lymphocytes . . . . .	46 per cent.
Large lymphocytes . . . . .	11 per cent.

Blood count (July 13, 1922):

Red blood cells . . . . .	4,800,000 per c.mm.
White blood cells . . . . .	13,000 per c.mm.

*Differential Blood Count:*

Polynuclear neutrophils . . . . .	32 per cent.
Small lymphocytes . . . . .	60 per cent.
Large lymphocytes . . . . .	8 per cent.

'Sections of the skin show only the ordinary signs of inflammation.'

Dr. Dyson has been good enough to give us a further report on his patient dated July 31, 1924. The redness was 'not nearly so marked, but although fainter in colour still covered almost the whole trunk'. The itching was less and the patient's general condition had improved. The differential blood count showed polynuclears 63 per cent., small lymphocytes 31 per cent., large lymphocytes 5 per cent., transitional 1 per cent., myelocytes 1 per cent.

*Commentary.*

The clinical features and blood-picture presented by this group of cases are characteristic. Of the five cases here described, four were in males. The youngest patient was 23 and the oldest 64. The most prominent physical sign in all cases was the generalized redness of the skin. Apparently, as in Case IV, this erythrodermia may begin with an eruption of striated and retiform character, suggesting to an expert the condition known as parakeratosis variegata. In this case alone have we obtained an authoritative description of the earliest stage. Ultimately the eruption in all cases becomes universal, the skin remaining of a peculiar red colour for years. This colour is well illustrated in Plates 10 and 11 (Cases II and IV). Although the tint varies from day to day, sometimes being darker (more purplish), there is a peculiar dull, pinkish red which we are able to recognize. The skin is slightly infiltrated and there is some scaling. Pruritus is a marked feature.

In the four cases personally seen by us, splenic enlargement was found once only. Glandular enlargement was present in all, but never formed the marked feature usual in chronic lymphatic leukaemia, of which affection a large localized mass of glands, or a great enlargement of the spleen, or both, is an almost constant accompaniment.

The course of the disorder is very chronic, extending over a number of years and unaffected by treatment.

The skin condition is associated with a blood-picture of peculiar type. Some degree of anaemia is usually present and may be fairly severe. The anaemia is of the secondary type, but the colour index may on occasion be high. The characteristic changes are found in the white cells, and consist in an increase relative and absolute of the lymphocytes, the type of lymphocyte involved being mainly the small lymphocyte. The total number of leucocytes varies from 8,000 to nearly 60,000, and of these numbers the small lymphocytes may form as much as 80 per cent. Such a blood-picture would appear to take its place between that of the common forms of secondary anaemia, in which we find a high relative lymphocytosis with leucopenia, and that of chronic lymphatic leukaemia. In the latter disorder we find a considerably higher total count as well as a somewhat greater relative proportion of lymphocytes. In the last sixteen cases of chronic lymphatic leukaemia seen by one of us (P. N. P.), the total cells averaged 96,300 and the lymphocytes 79.8 per cent. The total leucocytes in the five cases described here averaged 22,300 and the average percentage of lymphocytes was 63.7. In the earlier stages of this disorder the blood-picture might well pass either as normal or as that of a simple secondary anaemia, except for the very unusual combination of lymphocytosis with an increased total white count. In the latest stages the blood-picture approaches, but does not reach, that of leukaemia.

On clinical grounds the condition can easily be differentiated from *exfoliative dermatitis* (pityriasis rubra), where the flakes are abundant, and the skin is a brighter red and thinned rather than thickened. In *exfoliative dermatitis* we have never found a blood-picture in any way resembling that of the cases now under consideration.

In *mycosis fungoides* (granuloma fungoides) there may be a generalized erythrodermia both preceding and concomitant with the development of tumours. No tumours have been observed in any of the cases here described, although some of them have been watched for years. There is likewise no characteristic blood-picture in *mycosis fungoides* (4).

On examining the literature we find that Kaposi in 1885 described a condition which he named as lymphodermia perniciosa (5), and it has been suggested that our cases are instances of that affection. Kaposi's case was, we believe, one of *mycosis fungoides*, because there was tumour formation. The essential feature of his lymphodermia perniciosa is an eczematous condition which became generalized, and was associated with intense itching and followed by a marked thickening of the skin, upon which *ulcerating nodules* developed. The lymphatic







A woman aged 37 years developed an eczematous weeping eruption which in the course of some months covered the whole body. In spite of treatment the skin became thickened and was bright red, painful on pressure, and itching intensely. The lymphatic glands were enlarged. Leukaemia was diagnosed, the blood-count showing that the leucocytes were to the erythrocytes 1 in 24 to 1 in 26. The white cells were described as lymphocytes; there was no eosinophilia and very few leucocytes of pathological character. The skin is described as being red, thickened, and of leontiasis character *without* circumscribed tumours. The surface was scaly in some parts, weeping in others, with numerous excoriations and haemorrhages from scratching and perimaleolar oedema. After a temporary improvement under arsenic the patient died. The autopsy confirmed the diagnosis of leukaemia.

We suppose this case to be different from our own cases and that of von Zumbusch. It appears to us to be in all probability a case of acute myeloid leukaemia, on account of the marked increase in white cells, namely 1 to 24 red cells, while in our cases the leucocytosis is much less, being only 1-500 to 1-160. But in default of a more detailed description of the blood changes it is impossible to classify the case with confidence. At this date the distinction between myeloblast and lymphocyte was not appreciated, and in other respects the older accounts of blood changes are not sufficiently comprehensive to enable us to recognize the conditions described.

At a meeting of the Section of Dermatology and Syphilis of the New York Academy of Medicine on February 5, 1924, Dr. Walzer showed for Dr. Lapowski a man aged 62, whose condition appears to have been identical with that of our patients (10). The entire body is described as being of a peculiar dusky red, the skin slightly thickened, dry and pruriginous, and covered with scales; in front the scales were furfuraceous, and on the back thick, attached at the centre with the edge free. The skin of the hands and feet was thick and covered with rhagades. The nails were thick and heaped at the edges. The scalp was covered with thick whitish scales. All the glands were markedly enlarged. There was no enlargement of the liver or spleen. Numerous blood-counts were made. White cells about 10,000, with a lymphocytosis varying from 62 to 78 per cent. In the discussion it was pointed out that the condition differed from leukaemia and that the lymphocytosis was relative only. Reference was made to a fatal case of myeloid leukaemia of the skin, published by Drs. Ketron and Gay (11), in which there was a relatively low white cell count (10,000 to 64,000) associated with a characteristic eruption of nodular tumours, the cells of the nodules being myelocytes. In this case the lymphocytes in the blood did not exceed 5 per cent. The nodular lesions had the clinical and histological characters seen in the classical type of myeloid leukaemia which is usually associated with a white cell count of from 280,000 to 730,000.

A consideration of the complex here described brings us no solution of the connexion between the lymphæmia and the skin condition. We recognize a state of erythrodermia preceding the tumour stage of mycosis fungoides and

unaccompanied by changes in the blood. We have occasionally met with examples of leukaemia accompanied by local infiltrations of the skin. In the small group of cases described here the tumour formations of mycosis fungoides never developed, nor was the erythrodermia precisely identical in its clinical appearance. The blood state bore no resemblance to that of myeloid leukaemia, the type of leukaemia in which, in our experience, infiltration of the skin may occur. It did, however, approach that of lymphoid leukaemia, but at no stage of the complaint was a picture in any sense typical of leukaemia presented. Further, the erythrodermia developed quite independently of the lymphæmia. In the earliest stages the blood state scarcely differed from the normal; in later stages, when both erythrodermia and lymphæmia were well developed, skin sections showed that lymphocytic infiltration of the dermis was absent, and in only one case in sections of the skin examined *post mortem* was there an infiltration by lymphocytes beneath the epidermis. In this case sections of the skin taken at an earlier period showed no abnormality, and it would appear that the first sign of the disorder is an alteration in the colour of the skin, that the lymphocytosis appears later and gradually progresses, and that only in the very last stage a lymphocytic infiltration of the dermis takes place.

We would for the present place these cases in a category apart and distinguish them from other states of erythrodermia on the one hand and of leukaemia on the other. The condition is doubtless unusual, but since no less than five examples of it have come to our notice, we are confident that if the syndrome erythrodermia with lymphæmia is looked for, further cases will be disclosed.

## REFERENCES.

1. Sequeira, J. H., and Panton, P. N., *Brit. Journ. Dermatol. and Syphilis*, 1921, xxxiii, 391-400.
2. Dore, S. E., *ibid.*, 1922, xxxiv, 369.
3. Dyson, W., *ibid.*, 1922, xxxiv, 371.
4. Sequeira, J. H., *ibid.*, 1912, xxvi, 220.
5. Kaposi, 'Ueber eine neue Form von Haut-Krankheit: "Lymphodermia perniciosa",' &c. *Med. Jahrb.*, Wien, 1885, xv, 129. Translated, Doyon, *Ann. de Dermat. et Syph.*, Paris, 1885, 2<sup>e</sup> sér., vi, 400.
6. Danlos, *Ann. de Dermatol. et de Syphilol.*, Paris, 1902, 4<sup>e</sup> sér., iii, 1168; *ibid.*, 1903, 4<sup>e</sup> sér., iv, 239.
7. Sequeira, J. H., *Brit. Journ. Dermatol. and Syphilis*, 1911, xiii, 216.
8. von Zumbusch, L., *Archiv für Derm. u. Syph.*, Vienna, 1917, cxxiv, 1, 57. (This reference was only available after the war.—J. H. S.)
9. Riehl, *Trans. Second International Dermatological Congress*, Vienna, 1892, 156.
10. Walzer, *Archives of Dermatol. and Syphil.*, Chicago, 1924, x, 100.
11. Ketron and Gay, *ibid.*, 1924, vii, 176.



CASE IV.  
Late stage (1923).  
Reproduced by courtesy of  
DR. R. HUTCHISON.



CASE IV. Early stage (1922). From a water-colour drawing by DR. CRANSTON LOW's moulage  
by courtesy of DR. LOW.





CASE IV.  
Late stage (1923). Reproduced by courtesy of  
DR. R. HUTCHISON.



CASE II.





CHANGES IN THE BLOOD IN ANAESTHESIA<sup>1</sup>

By DOROTHY G. E. POTTER

(From the Department of Therapeutics, University of Edinburgh)

*Introduction.*

MUCH work has been done on the fall in the bicarbonate reserve which, as numerous workers have shown, occurs during anaesthesia both in human subjects and in animals, but that fall has never been explained, so that there are still many directions in which inquiry may be made.

Caldwell and Cleveland (1), using Van Slyke's method, studied the effect of various anaesthetics on the alkaline reserve in the plasma of 120 patients. They could not prove any relationship between the decreased reserve and the excretion of acetone bodies in the urine. They also found that there was a negligible difference in the diminution caused by the various anaesthetics used, though the return to normal was somewhat slower after chloroform.

Cullen, Austin, Kornblum, and Robinson (2), working with dogs point out that the larger part of the fall occurs during the first few minutes of anaesthesia. It will be shown in the present paper that marked changes in other constituents of the blood have occurred in patients who have only been anaesthetized for a few minutes.

Although no definite relationship has as yet been made out, it seems that the metabolism of sugar and phosphate in the body is intimately bound up. Asphyxia or anoxaemia causes a rise in both; sugar has long been known to increase in asphyxia, and J. B. S. Haldane, Wigglesworth, and Woodrow's (3) experimental work has shown that the blood phosphates rise after breathing 6-7 per cent. carbon dioxide for a considerable period.

Both sugar and phosphate fall after insulin injections. Winter and Smith (4) produced convulsions in rabbits and then brought about recovery by various means. It is significant that they find that 'after recovery with adrenalin, inorganic phosphate, as a rule, rose along with the sugar. Later, however, the value for phosphate fell, whereas the blood sugar had reached a height usually above normal'.

In a recent paper Stehle and Bourne (8) have estimated the phosphorus content of muscle, liver, and brain in anaesthetized and control animals, and found a reduction in the total phosphorus content of muscle, and an increase in

<sup>1</sup> Received November 11, 1924.

the liver of animals killed after anaesthesia, whereas that of the brain remains much the same. Since the amount of bases (estimated as sodium and potassium sulphate) does not appear to undergo much change, they put forward the suggestion that phosphoric acid leaves the muscles during anaesthesia and accumulates in the liver, because the excreting power of the kidneys is depressed. They did not find much alteration in the pH of the tissues concerned, and no work was done on the sugar content.

As the metabolism of sugar and blood phosphate seems undoubtedly to have some relationship, the following hypothesis is put forward in this paper: that the phosphoric acid leaves the muscles as a hexose phosphoric acid,  $C_6H_{10}O_4(H_2PO_4)_2$ . Embden and other workers have shown that this compound exists in muscle. This combines with part of the blood alkali and contributes to the fall in the alkaline reserve. Blatherwick, Bell, and Hill (13) suggest that this hexose phosphoric acid is intermediary between glycogen and lactic acid. In recovery from anaesthesia part of this compound may revert to glycogen and part be excreted as phosphates in the urine.

The loss of hexose phosphoric acid would not alter the pH of the muscles beyond the range of experimental error. Perhaps this hexose phosphate (which is split up in laboratory methods of analysis) does not supply the patient with glucose in a form in which it can be assimilated, and the partial tissue starvation may account for some of the post-operative symptoms. Stehle and Bourne were not able to prove that it is phosphoric acid which leaves the muscles, nor whether the combination was organic or inorganic, since they only estimated the total phosphorus content.

It is not suggested that changes in the blood phosphate have more than a part share in the fall in the bicarbonate reserve that occurs; Reimann and Bloom (12) take the view that the formation of blood acetone bodies accounts for 20-100 per cent. of the bicarbonate fall observed, on an average for 60 per cent. Haemoglobin has a great deal to do with the carriage of carbon dioxide and adjusting the pH of the blood. Stewart Ross, in the introduction to his *Handbook on Anaesthetics*, states that 'reaching the blood-stream by absorption from the lung alveoli, the drug (anaesthetic) enters into loose combination with the red blood corpuscles and a small proportion only is carried by the plasma. Within the corpuscles it must of necessity displace a certain proportion of oxygen normally carried. This factor is of great importance only in the case of  $N_2O$ , which readily displaces the larger part of the normal oxygen content. In other anaesthetics the same process occurs, but to a less degree.' This seems to bear out Crile's view that the lowering of oxygenation is the true cause of anaesthesia.

Cullen, Austin, Kornblum, and Robinson (2) state that 'anoxaemia alone without exertion lowers the alkaline reserve, but less than does the administration of anaesthetics', and they also conclude that in anaesthesia 'we are dealing with an uncompensated acidosis and not a "compensated alkalosis"'.

The rise in the threshold of the respiratory centre for carbon dioxide in

anaesthesia (Yandell Henderson and Scarbrough (6)) may have something to do with determining the rise of blood phosphate; for, as experiments quoted below will show, the rise does not invariably take place in anaesthesia. The buffering between alkaline and acid phosphate could not be shown unless all the various bases present in the body were taken into account, since it is estimated as phosphate.

Stehle and Bourne have not found changes in the sodium or potassium content of liver and muscles, though in a previous paper (7) they found an increased excretion of these bases in the urine in the post-anaesthetic period. The bicarbonate undergoes rapid fluctuation, but there is still calcium and ammonia. Calcium does not appear to have been studied in relation to anaesthesia. J. B. S. Haldane (personal communication to author) found that breathing 6-7 per cent. carbon dioxide raised the blood calcium slightly. The ammonia of the blood has not been found to be abnormal, though an increased excretion may occur for the first few hours after anaesthesia.

If hexose phosphoric acid enters the blood, owing to the numerous factors involved, it is not to be expected that it could be proved by trying to work out a relationship between the phosphate and sugar increase. For the blood-sugar might quite well rise independently, as in Winter and Smith's experiment quoted above. As regards the hyperglycaemia which occurs in anaesthesia, there are several factors to be taken into account. Ross and McGuigan (10) state that ether itself is responsible for the greater part of the blood-sugar change and not asphyxia or excitement. Asphyxia in an ordinary well-given anaesthetic should not occur to such a degree as to influence the blood-sugar *per se*, and, as these authors also point out, the fact that the increase continues after the cessation of anaesthesia argues against hyperglycaemia being due to asphyxia.

#### *Method.*

Whole blood was used in every instance for several reasons, one being that to estimate phosphates, carbon dioxide combining power, and sugar, at least 14 c.c. of blood is needed, and a similar amount of plasma would need a larger quantity of blood than the surgeon, in many instances, would be prepared to permit his patient to lose.

To prevent haemolysis, a test-tube containing a few milligrams of potassium oxalate and a knife-point of sodium fluoride was placed in a flask of ice. The blood was drawn without stasis, and placed directly from the syringe into the tube. The inorganic phosphate and carbon dioxide combining power estimations were proceeded with at once.

For estimations of phosphate, both inorganic and total acid-soluble, Fetter's (5) gravimetric method was used. In many cases, the hydrolysable phosphate was estimated by boiling 10-15 c.c. of the trichloroacetic acid filtrate for two hours (Zucker and Gutman (16)), then precipitating and estimating as inorganic phosphate by Fetter's gravimetric method.

A definite fraction of the total acid-soluble phosphate seems to be thus hydrolysed, though its significance is not yet clear. The reason for estimating the hydrolysable phosphate was that, if the rise in inorganic phosphate which has been found in the cases just after anaesthesia were due to haemolysis taking place, the hydrolysable fraction would be decreased instead of increased, as has been found. Hamburger and Ewing (9) worked at the subject of haemolysis in post-anaesthetic conditions. They found no material increase with  $N_2O$  or ether, but a definite increase after chloroform. Blood-sugar estimations were done by Benedict's picro-picrate method (14). The alkaline reserve was estimated on whole blood by a technique practically identical with that used by Christiansen, Douglas, and Haldane (15). The alkaline reserve is obtained by expressing as a percentage of the normal the difference between volume per cent. carbon dioxide found, and the normal volume of carbon dioxide, which is taken as that of Haldane's blood. But normal blood may show a curve below this, though only once have I found a result above the normal, and the patient had then not had more than a three-hour fast.

The first specimen of blood in several cases was taken between 9 and 10 a.m., one to two hours before operation; estimations were carried out immediately. A second specimen was taken immediately after operation. In every case except one (where no morphia was given) the patient was quite flaccid and the blood was noted to be of a bright red, almost arterial, tinge.

#### *Observations and Discussion.*

The observations for this paper were carried out over a period of eight months ending in March 1924; in every case studied, unless otherwise stated, the anaesthesia was induced by  $C_2E_3$  mixture, and continued with ether. A note was made of the approximate amount of anaesthetic used; but in the open method this is not the actual amount the patient received, a variable quantity being lost by evaporation. It was not found that either the amount used or the duration of the anaesthesia had any bearing on the extent of the fall in the bicarbonate reserve.

Crile has pointed out the starvation factor in operation cases where prolonged pre-operative starvation and drastic purgation produce a slight lowering of the bicarbonate reserve before the anaesthesia is begun. The cases studied received a light luncheon, tea, and supper on the day before, and a cup of tea at 5 a.m., so that starvation was reduced to a minimum beforehand.

All cases were from a gynaecological ward, and were selected as being fairly normal women who would be likely to come through the operation in a normal manner. No case chosen happened to have more than an average amount of post-operative vomiting or excessive amounts of acetone bodies excreted in the urine.

Morphia causes a hyperglycaemia and would be a contributing factor in the cases studied; for they received as a routine measure just before operation a

hypodermic injection of morphia gr.  $\frac{1}{4}$  and atropin sulphate gr. 1/150th. Its effect on the blood phosphate does not appear to have been tried, though no change is to be expected.

Control experiments as to the effect of morphia and atropin alone were carried out on two convalescent women. They received diet and purgation similar to pre-operative treatment and were each given an injection of morphia and atropin. Specimens of blood were taken beforehand. The phosphate and alkaline reserve estimations were carried out at once. The injection was then given and a further specimen of blood taken about thirty to fifty minutes after injection.

Table I. The changes in the phosphate are within range of experimental error. In the second experiment the morphia has caused an increase in the alkaline reserve, as Hjort and Taylor (11) have observed it to do in animals. This patient was extremely drowsy after her injection and vomited frequently later on in the day. In both experiments there is a rise in the blood-sugar.

Table II. In one case no injection of morphia or atropin was given prior to operation. Although there was no history of nephritis and no albuminuria she seemed to have a high blood phosphate and sugar. She was exceedingly difficult to anaesthetize, struggling a good deal during induction of anaesthesia, and at the time of taking the second specimen of blood her arm was slightly rigid. The change in the phosphate content is very slight, but it will be seen that each is slightly lower in the post-operative specimen.

Table III gives details of seven cases done immediately before and immediately after operation. In each case the patient received an injection of morphine hydrochloride gr.  $\frac{1}{4}$  and atropin sulphate gr. 1/150th just prior to operation. Anaesthesia was induced by  $C_2F_6$  mixture and continued with ether.

In five of the seven cases a rise occurred in the inorganic phosphate, and, since the hydrolysable fraction is also increased, it seems to show that it is the inorganic part which is altered, and that the total acid-soluble phosphate rise occurs because the inorganic fraction is included in the total.

Caldwell and Cleveland (1) found a diminution of from 3.1 to 4.7 volumes per cent. in the plasma alkaline reserve in the twenty-four hours prior to operation, which was probably due to fasting and purgation. They found a further diminution of from 3.3 to 5.3 volumes per cent. during anaesthesias of forty-four to fifty-eight minutes. Table III shows a diminution in each case of from 3 to 10 volumes per cent. in the whole blood during short periods of anaesthesia. In Case C. 1 there was a drop of 5 volumes per cent. with an anaesthesia lasting thirty-five minutes and only a slight change in the blood phosphate content, whereas in Case C. 2, with a period of anaesthesia lasting only ten minutes, the alkaline reserve dropped 7 volumes per cent. and there was a marked rise in all three phosphate fractions. In no case studied was the decrease in the alkaline reserve so great as to reach the point where symptoms of acidosis intervene.

Table IV, although a small series, also seems to bear this out. In these cases the total fat, haemoglobin, and total acid-soluble phosphate were estimated



before and after anaesthesia. Variations in the first two are bound to affect the total acid-soluble phosphate, since the larger portion of the organic phosphorus is included in the corpuscles and the total fat content includes at least 90 per cent. of the lecithin phosphorus.

Hamburger and Ewing (9) found a slight fall in haemoglobin after anaesthesia which was transient and ascribed as due to accompanying asphyxia and not a result of the anaesthetic. Haemoglobin estimations shown in Table IV were done by Haldane's haemoglobinometer and carried out in duplicate. Except in one case, each shows a reduction of 1 to 3 per cent. No parallelism between the changes in the acid-soluble phosphorus and the haemoglobin percentage was found.

Wigglesworth and Woodrow (17) have found that the ingestion of 100 gm. of glucose causes no measurable change in the organic acid-soluble phosphorus of the blood. Some observers consider that a hexose phosphate forms part of the acid-soluble phosphorus. Our view is that if a transference of hexose phosphate takes place from muscle to liver via the blood, the hexose phosphate breaks up and the phosphate joins up to and increases the inorganic blood phosphate.

In one case a drop has occurred in the total acid-soluble phosphate and total fat. In Case 4 the total acid-soluble phosphate has risen, whereas the fats are practically level.

Table V. Owing to the conflicting ideas with regard to the giving of sodium bicarbonate, glucose, &c., before and after operation, some experiments with special pre-operative treatment were carried out. Patients were given large doses of sodium bicarbonate or glucose, or both, to see if it affected the blood phosphates before and after anaesthesia. Sodium bicarbonate ingested to the extent of 60 gm. causes no significant changes in blood phosphate (3). The first patient, Mrs. E., showed a considerable increase in both blood phosphate and sugar. After operation her urine contained a trace of acetone and she vomited only slightly. Mrs. McD., who received the same treatment (no blood analyses done), vomited once about two hours after operation, but her urine contained quite large amounts of acetone and diacetic acid for the first day or two.

Table VI. These patients were observed at the beginning of the investigation; the specimens of blood were taken between 11 and 12 in the morning, generally on the day following operation, and again when the patient had returned to the usual diet. It will be seen that the alkaline reserve does not return to normal immediately, but the blood phosphate estimations do not show any constant results.

Table VII. The urinary phosphates were estimated in several patients, using the ordinary uranium titration method. In every instance it will be seen that there was a greatly increased output in the first few hours after anaesthesia. This increase occurs irrespective of the presence or of the absence of acetone bodies.

The acidity of the urine was estimated according to Cole's method (Cole's



*Physiological Chemistry*, p. 275) by titrating the urine with N/10 sodium hydroxide to a pH of 7.45, using phenol red as an indicator. The increased acid excretion has not been found to run parallel with the increased excretion of  $P_2O_5$ .

When the  $P_2O_5$  and ammonia excretion have been calculated as milligrams per hour, the patient has been catheterized at the times noted. Although the rate of excretion thus calculated can only be approximate, it will be seen that an increased rate of excretion occurred in both the urinary phosphate and ammonia. Collip (18) found the rate of secretion of ammonia slightly increased in nine cases and diminished in six. The pH expressed in terms of N/10 acid was also increased. This increase occurred irrespective of the presence of acetone bodies.

The conclusion one comes to on finding the blood phosphate raised after a short period of anaesthesia is that the rise takes place in order to assist the body to get rid of the abnormal amounts of acid which are present in the body to a greater or less degree after an anaesthetic has been administered. That an increase of acid is found in the blood is shown by the lowering of the alkaline reserve and increase of the H-ion concentration. When the phosphates are mobilized either in the blood or as an accumulation in the liver, the kidney is enabled to take its share in excreting acids from the body.

#### *Summary.*

1. The observation made by Cullen, Austin, Kornblum, and Robinson (2) in animals, that the fall in alkaline reserve under ether and chloroform occurs in the first few minutes of anaesthesia, has been confirmed in patients. In one subject with an anaesthesia lasting only 10 minutes a decrease of 7 volumes per cent. in the alkaline reserve occurred.

2. The duration of the anaesthesia has no relation to the change in the blood phosphate nor to the fall in the alkaline reserve.

3. The rise in the blood phosphate, when it occurs, is due to the inorganic radical; the rise found in the hydrolysable and total acid-soluble fractions is simply owing to the inorganic portion being included in the latter two.

4. Although no relationship can be made out, it is suggested in this paper that the increase in blood phosphate that occurs in anaesthesia may be due to the passage from the muscles to the blood of a hexose phosphoric acid compound. This has some small share in the lowering of the alkaline reserve, and accounts for the loss of phosphorus which other observers have found to occur in the muscle of anaesthetized animals, and which is stored by the liver until the kidney is capable of excreting the accumulated waste products. The kidney needs phosphate in order that it may excrete the excess of acid accumulated in the body whilst its excretory capacity was diminished by the anaesthesia, so that the excess of phosphorus found in the liver may have been mobilized to assist in the excretion of acid.

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## REFERENCES.

1. Caldwell and Cleveland, *Surg. Gynec. and Obstet.*, Chicago, 1917, xxv. 22.
2. Cullen, Austin, Kornblum, and Robinson, *Journ. Biol. Chem.*, Baltimore, 1923, lvi. 625.
3. Haldane, J. B. S., Wigglesworth, and Woodrow, *Proc. Roy. Soc., Lond.*, 1923-4, xcvi. 1. B.
4. Winter and Smith, *Journ. Physiol., Camb.*, 1923-4, lviii. 327.
5. Fetter, *Archiv. Int. Med.*, Chicago, 1923, xxxi. 413.
6. Henderson, Yandell, and Scarbrough, *Amer. Journ. Physiol.*, Boston, 1910, xxvi. 260.
7. Stehle, Bourne, and Barbour, *Journ. Biol. Chem.*, Baltimore, 1922, liii. 341.
8. Stehle and Bourne, *ibid.*, Baltimore, 1924, lx. 17.
9. Hamburger and Ewing, *Journ. Amer. Med. Assoc.*, Chicago, 1908, li. 1586.
10. Ross and McGuigan, *Journ. Biol. Chem.*, Baltimore, 1915, xxii. 407.
11. Hjort and Taylor, *Journ. Pharmacol. and Exper. Therap.*, Baltimore, 1919, xiii. 407.
12. Reimann and Bloom, *Journ. Biol. Chem.*, Baltimore, 1918, xxxvi. 211.
13. Blatherwick, Bell, and Hill, *ibid.*, Baltimore, 1924, lxi. 241.
14. Benedict, *ibid.*, Baltimore, 1918, xxxiv. 203.
15. Christiansen, Douglas, and Haldane, *Journ. Physiol., Camb.*, 1914, xlviii. 244.
16. Zucker and Gutman, *Proc. Soc. Exper. Biol. and Med.*, New York, 1921-2, xx. 133.
17. Wigglesworth and Woodrow, *Proc. Roy. Soc., Lond.*, 1924, xcv. 558. B.
18. Collip, *Brit. Journ. Exper. Path.*, Lond., 1920-1, i. 282.

TABLE I. Whole Blood. Effect of Morphia and Atropin Injection.

Case.	Time.		Inorganic Phosphate. Mg. %.	Acid-soluble total Phosphate. Mg. %.	Sugar. Mg. %.	Alkaline Reserve. %.
A. H., aged 20	9.50 a.m.	—	5.5	44.7	90	—
	10.34 a.m.	Injection, morphia and atropin	—	—	—	—
	11.20 a.m.	—	5.3	42.9	96	—
J. C., aged 22	9.45 a.m.	—	3.6	44.5	98	-12
	10.49 a.m.	Injection, morphia and atropin	—	—	—	—
	11.20 a.m.	—	3.8	44.5	112	± 0

TABLE II.

Case: Mrs. McM.—Duration of Anaesthesia—15 minutes. C<sub>2</sub>E<sub>3</sub> and ether.  
Operation: Dilatation and curettage; cauterization of cervix.

BLOOD. Time.	Inor- ganic. Mg. %.	Hydro- lysable. Mg. %.	Total Acid- sol. Mg. %.	Sugar. Mg. %.	c.c. vol. % CO <sub>2</sub> taken (Haldane).	Alkaline Reserve. %.	URINE. Time.	P <sub>2</sub> O <sub>5</sub> grm. %.		NH <sub>3</sub> N grm. %.		pH in terms of N/10 Acid %.	Ace- tone.
								Amount. c.c.	Per Hour.	Amount. c.c.	Per Hour.		
1st speci- men 9.35 a.m.	6.9	17.0	38.5	263	44.5	49	Before operation: 9.35 a.m. 11.50 a.m. After operation: 2.30 a.m. 8 a.m.	—	0.075	0.021	—	15 30	nil nil
2nd speci- men 12.10 p.m.	6.3	13.2	36.9	333	39.5	49		50	0.150	0.042	0.004	50 50	trace trace

TABLE III. Whole Blood. Taken immediately before and immediately after operation.

Name.	Before Opera- tion.	After Operation.	Phosphate.			Sugar. Mg. per 100 c.c.	c.c. vol. % CO <sub>2</sub> taken up.	c.c. vol. % CO <sub>2</sub> normal (Haldane).	Alkaline Reserve. %.	Anaesthesia.	Type of Operation.	Remarks.
			Inor- ganic. Mg. per 100 c.c.	Hydro- lysable. Mg. per 100 c.c.	Total. Mg. per 100 c.c.							
C. I	9.10 a.m.	—	2.5	7.7	37	133	44.3	52.4	-16	11.20 a.m. Injection, morphia and atropin	Amputation of cervix	Vomiting just before 3rd speci- men of blood was taken
		11.55 a.m.	2.8	8.3	36	160	39.5	50.2	-21	11.20 a.m.-11.55 a.m. C <sub>2</sub> E <sub>3</sub> mixture, 120 c.c. O <sub>2</sub> also administered	Pelvic floor repair	
		24 hours	3.3	10.7	36.9	127	38	46.9	-18			Acetone + for 2 days afterwards

TABLE III (continued).

Name.	Before Operation.	After Operation.	Phosphate.			Sugar. Mg. per 100 c.c.	c.c. vol. % CO <sub>2</sub> taken up.	c.c. vol. % CO <sub>2</sub> normal (Haldane).	Alkaline Reserve. %.	Anaesthesia.	Type of Operation.	Remarks.
			Inor- ganic. Mg. per 100 c.c.	Hydro- lysol. Mg. per 100 c.c.	Total. Mg. per 100 c.c.							
B. 1	9 a.m.	—	4.3	—	—	—	46.6	50.9	-8	11 a.m. Injection, morphia and atropin	Retroversion of uterus	Anaesthesia taken 8 hours after
		12 noon	6.3	—	42	137	39.87	49	-18	11.25 a.m.-11.55 a.m. C <sub>2</sub> E <sub>3</sub> 26 c.c., ether 150 c.c.	Gilliam operation	Acetone + Acetone
		18 days	3.5	—	38	134	47.6	51	-8		Inguinal hernia	Acetone + Acetone
B. 2	9 a.m.	—	—	—	42.5	121	53.87	57.2	-10	11 a.m. Injection, morphia and atropin	Left ovario- tomy	Acetone negative each day
		12.10 p.m.	5.8	19.0	49.4	190	42.7	51.4	-17	11.10 a.m.-12.10 p.m. Anaesthesia—amount not stated		
		16 days after	3.0	—	42.5	—	53.4	53.8	±0			
I.	9.25 a.m.	—	4.2	10.5	46.8	170	47.5	49	-3	1.10 p.m. Injection, morphia and atropin	Dilatation and curet- tage	Acetone tr. 6 hours after
		1.40 p.m.	4.2	16.0	50.0	180	46.0	49	-6	1.23 p.m.-1.38 p.m. C <sub>2</sub> E <sub>3</sub>		
		24 hours	3.3	—	46.1	—	—	—	—			
C. 2	9 a.m.	—	4.8	5.0	43.7	—	50.33	51.4	-2	12.45 p.m. Injection, morphia and atropin	Dilatation and curet- tage	Acetone + first day
		1.15 p.m.	6.3	7.7	57.3	—	45.7	49.6	-9	12.58 p.m.-1.8 p.m. C <sub>2</sub> E <sub>3</sub> 7 c.c., ether 60 c.c.		
		—	4.9	11.2	33	129	50.2	50.4	±0	11.30 a.m. Injection, morphia and atropin	Incomplete abortion	Acetone + first day
W.	9.40 a.m.	—	5.3	13.4	39	156	45.8	50.0	-8	12.15 p.m.-12.35 p.m. C <sub>2</sub> E <sub>3</sub> 7 c.c., ether 120 c.c.	Dilatation and curet- tage	
		12.40 p.m.	—	—	—	—	—	—	—			
		—	3.1	—	35.8	—	—	—	—	11 a.m. Injection, morphia and atropin	Umbilical hernia	
B. 3	9.45 a.m.	12 noon	4.1	—	39.1	—	—	—	—	11.10 a.m.-11.55 a.m. Anaesthesia—amount not noted		

Cases marked B. 1, I., and W. have had urinary estimations done as well.

TABLE IV. Whole Blood before and after Operation

Patient.	Haemoglobin.		Total Acid-soluble Phosphorus.		Total Fat.		Cholesterol.		Duration of Anaesthesia. Minutes.
	Before. %.	After. %.	Before. Mg. %.	After. Mg. %.	Before. Mg. %.	After. Mg. %.	Before. Mg. %.	After. Mg. %.	
1	87	85	40.3	44.7	684	786	225	227	15
2	94	93	40.1	31.3	933	798	216	210	30
3	60	60	32.3	35.8	943	955	—	—	35
4	93	90	48.1	51.0	1228	1219	239	221	60
5	86	82	39.0	44.0	918	920	—	—	25

TABLE V. Cases receiving Special Pre-operative Treatment.

Case.	Time.	Phosphates.				Alkaline Reserve. %.	Hb. %.	Remarks.
		Inorganic. Mg. %.	Hydrolyzable. Mg. %.	Total Acid-sol. Mg. %.	Sugar. Mg. %.			
E.	9.45 a.m.	4.7	—	38	105	—	63	Previous evening, 7 p.m. Glucose, grm. 50
	Period of operation 11.55-12.24 p.m.							Morning of operation, 5 a.m. Glucose, grm. 30
	12.30 p.m.	6.2	—	43.6	125	—	68	" " Anaesthesia 30". C <sub>2</sub> F <sub>3</sub> , 7.5 c.c. Ether, 120 c.c.
W.	9.30 a.m.	4.0	—	—	114	+4	—	Previous day, 12 noon, 3 and 6 p.m. Sod. bicarb., grm. 2
	Period of operation 11-11.25 a.m.							Morning of operation, 5 a.m. Glucose, grm. 50; Sod. bicarb., grm. 2
	11.30 a.m.	5.8	—	—	148	-10	—	Chloroform, examination—Anaesthesia 25". C <sub>2</sub> F <sub>3</sub> , 15 c.c. Ether, 60 c.c.
N.	10 a.m.	3.5	8.9	30.2	105	-6	—	Previous evening, 7 p.m. Glucose, grm. 50, in addition to supper
	11.45 a.m.	4.2	11.7	33.5	167	-21	—	Day of operation, 5 a.m. Glucose, grm. 30
								" " 8 a.m. Glucose, grm. 30

TABLE VI. *Urine Estimations in Post-operative Cases.*

Name.	Before.	After.	P <sub>2</sub> O <sub>5</sub> .		NH <sub>3</sub> .		pH in terms of N/10 Acid %.	Acetone.	Remarks.
			Mg. %.	Mg. per hour.	Mg. %.	Mg. per hour.			
P.	—	5 a.m. 1st day	532	—	—	—	—	+	—
		5 a.m. 2nd day	256	—	—	—	—	+	—
		5 a.m. 3rd day	213	—	—	—	—	—	—
McK.	—	5 a.m. 1st day	584	—	—	—	—	+	—
		5 a.m. 2nd day	292	—	—	—	—	—	—
		5 a.m. 3rd day	40	—	—	—	—	—	—
		5 a.m. 4th day	120	—	—	—	—	—	—
S.	6 hours	—	8	—	—	—	—	—	—
		5 a.m. 1st day	737	—	—	—	108	—	—
B. R.	—	5 a.m. 2nd day	256	—	—	—	48	—	—
		5 a.m. 1st day	325	—	—	—	40	+	—
B. I	8 a.m. 10.25 p.m.	5 a.m. 2nd day	224	—	—	—	33	—	—
		—	7.5	—	—	—	—	—	Shows a low percentage of phosphate excretion in the morning hours, before operation
		8.15 p.m. same day	7.5	—	—	—	20	—	
L.	8.50 a.m. 1.10 p.m.	10.15 a.m. day after	610	—	—	—	101	+	Both P <sub>2</sub> O <sub>5</sub> and acid excretion greatly increased 6 hours after
		—	495	—	—	—	9.2	—	
		—	20	—	9.45	—	2	—	Shows increased percentage of P <sub>2</sub> O <sub>5</sub> , NH <sub>3</sub> , and pH, partly due to increased concentration of urine as seen by raised specific gravity
		7 p.m. same day	14	7	9.2	4.6	3	—	
W.	11.25 a.m.	2.15 a.m. next day	460	69	40.0	6.0	56	trace	Case showed a high ammonia excretion before operation, yet alkaline reserve was normal. No glycosuria
		—	392	61	50.0	7.8	96	—	
		6.30 p.m.	185	—	67	—	42	—	
		2.45 a.m.	360	115	13.3	13.8	64	+	
H.	11.40 a.m.	—	510	116	45	10.3	80	+	
		7.30 p.m.	72	—	9.45	—	16	—	
		4.15 a.m.	550	—	—	—	82	trace	
McD.	—	—	—	—	31.5	—	112	trace	
		5 a.m. 1st day	495	—	—	—	165	—	
		5 a.m. 2nd day	308	—	—	—	50	—	
		5 a.m. 3rd day	86	—	—	—	28	—	

TABLE VII. *Whole Blood. Post-operative Cases.*

Phosphates.



# CHANGES IN THE BLOOD IN ANAESTHESIA

273

TABLE VII. Whole Blood. Post-operative Cases.

Case.	Time of taking Specimen.	Phosphates.			Sug. Mg. %.	c.c. vol. % CO <sub>2</sub> taken up.	c.c. vol. % CO <sub>2</sub> normal (Haldane),	Alka- line Re- serve. %.	Duration and Type of Anaes- thesia.	Post-anaesthetic Period.
		Inor- ganic. Mg. %.	Hydro- lysable. Mg. %.	Total. Mg. %.						
P.	24 hours after operation	5	—	49	111	39.2	51.5	-24	—	See Case P. on Urine Table VI. Ace- tone + for first 2 days after. Di- minishing excretion of P <sub>2</sub> O <sub>5</sub> in urine. Vomiting just before first blood specimen was taken
	6th day "	3.2	—	44.7	—	—	—	—	—	
McK.	24 hours "	6.5	—	41	142	—	—	—	—	See Case McK. on Urine Table VI.
	8th day "	4.4	—	41	—	—	—	—	—	No post-operative vomiting
A.	24 hours "	3.2	—	44.3	—	51.8	54	-5.4	—	No post-operative vomiting
	8th day "	4.0	—	40.6	—	—	—	—	—	
B. R.	24 hours "	3.6	—	43.9	125	44.4	50	-14	Pelvic floor	See Case B. R. on Urine Table VI.
	48 "	5.5	—	53	—	50.4	52.4	-4	repair.	Acetone + + 14 hours after operation
							180 c.c.		30" C <sub>2</sub> E <sub>3</sub> .	
P.	24 hours "	5.0	—	41	140	42.5	50.2	-14	70"	Acetone + + first day after. Slight post-operative vomiting. Acetone neg. 2nd day after
	5th day "	3.3	—	36	182	50	53	-6	—	
H.	Immed. "	6.1	12.9	41.6	235	40.38	49.6	-18	—	See Case H. on Urine Table VI. No acetone in urine. No glycosuria in spite of high blood-sugar. Erythe- matous rash 24 hours after opera- tion
	24 hours "	6.7*	9.4	38.5	232	46.0	49	-6	25"	* Possibly slightly hydrolysed; hydro- lysable fraction is lower than pre- operative one. Very slight post- operative vomiting
	7th day "	4.6	12.0	34.6	230	54.5	50	+9	—	
	(Only 3 hours' fast)									
McD.	24 hours after operation	3.5	—	—	—	46	51.9	-11.5	—	See Case McD. on Urine Table VI.
	48 "	2.9	—	—	—	44.1	51.1	-13.8	—	Slight post-operative vomiting. Ace- tone trace first day after operation
	72 "	3.7	—	—	—	45.4	51	-11	—	
	96 "	4.9	—	—	—	—	—	—	—	
	(3 hours' fast)									
S.	Before operation	3.9	—	39.5	—	43.4	50.9	-14	50".	See Case S. on Urine Table VI. Slight post-operative vomiting. No acetone excreted in urine
	24 hours after operation	4.4	—	41.6	—	46.2	53.8	-14	pair of pel- vic floor.	
	48 "	3.9	—	34.7	—	43	50.7	-14	C <sub>2</sub> E <sub>3</sub> .	Large excretion of P <sub>2</sub> O <sub>5</sub> in urine 24 hours after operation
									30 c.c. Ether, 240 c.c.	

[Q. J. M., April, 1925.]

## THE TOLERANCE OF THE BODY FOR UREA IN HEALTH AND DISEASE<sup>1</sup>

By H. E. ARCHER AND G. D. ROBB

(From the Biochemical Laboratory of the West London Hospital)

THE illumination afforded by glucose tolerance tests in patients with disordered carbohydrate metabolism suggested the application of a similar test with urea in patients with disordered kidney function. A dose of glucose by mouth is taken in the first case, and one of urea in the second. The subsequent changes in the blood and in the urine are observed.

The two processes, of course, differ in several respects. Glucose is present in the blood with a view to storage or utilization, and is excreted only when its level rises above a certain point, usually about 0.18 per cent. Urea, on the other hand, is present in the blood only to be excreted. It is an undesirable substance, which the kidneys are voiding as rapidly as is convenient. In spite of this constant discharge, however, its level never falls much below 0.02 per cent., and usually remains between that point and 0.04 per cent.

The actual level of the urea, or of the total non-protein nitrogen, in the blood has been well studied in health and disease. A rise in the value is found in many conditions, chiefly in renal deficiency, though unexpected results often occur. A high value is occasionally found when the clinical condition of the patient causes no alarm, and sometimes the value lies within normal limits when a severe or even hopeless degree of renal insufficiency is present.

It was thought possible that a study of the tolerance of the body for urea might prove of value, perhaps as an index of the efficiency of the kidneys in cases of known or suspected renal damage.

Both normal and abnormal individuals were investigated. Amongst the latter, the severe and definite types were studied, as well as those showing evidence of slight or uncertain kidney mischief.

The whole of the work was done in the Wards, Out-patient Department, and Biochemical Department of the West London Hospital.

### *Methods employed.*

A. *In the wards.* The usual investigations on a renal case are carried out. Arterio-sclerosis and retinitis are looked for. The state of the heart and blood-

<sup>1</sup> Received December 20, 1924.

pressure is ascertained. The urine is examined for blood, sugar, albumin, pus, and casts.

*The urea tolerance test and urea concentration test are carried out simultaneously.* The patient takes nothing after 9 p.m. save tea and toast at 6 a.m. He passes water about the same time.

*The tests are started at any convenient time, usually 8-30 or 9 a.m., when the patient empties the bladder and the urine is saved.* A specimen of blood is taken. The patient drinks 15 grm. of urea dissolved in 3 ounces of water flavoured with *Tr. aurantii*.

*Subsequent specimens of blood are taken 30, 60, 120, and 240 minutes after urea is taken.*

In serious renal cases the 30 and 120 minute specimens may be dispensed with.

*Subsequent specimens of urine are taken 60, 120, and 180 minutes after urea is taken.*

B. *In the laboratory.* The estimation of urea in the blood is done by the micro method previously described by one of us (H. E. A.) (1). 0.2 c.c. of blood is required, and may be collected directly from the finger, after pricking with a needle, into a graduated pipette, or the blood may be taken from a vein and placed in an oxalated tube. The urea does not tend to disappear from either fresh or oxalated blood. The actual estimation may thus be postponed for 24 hours if necessary.

0.2 c.c. of blood is incubated with 0.3 c.c. of a solution of urease (one tablet of Dunning's urease in 10 c.c. of water) and 1 c.c. of water, at 50° C., in a water-bath for 15 minutes. The proteins are precipitated by 0.3 c.c. of 10 per cent. sodium tungstate and 0.3 c.c. of 2N/3 sulphuric acid. The solution is diluted to a volume of 8 c.c. and centrifugalized. 5 c.c. of the supernatant fluid are mixed with 5 c.c. of water, and 2 c.c. of Nessler's reagent added. The resulting yellow or brown colour is compared in a Kober colorimeter with a standard solution of ammonium sulphate, 1 c.c. of which, with 9 c.c. of water and 2 c.c. of Nessler's reagent, gives a colour equivalent to that produced by 0.0001 grm. of urea.

Without a micro method of this sort the present investigation would have been impossible. The small amount of blood required causes the patient no more discomfort than does the sugar-tolerance test.

*The urea in the urine is estimated by the hypobromite method.*

### *The Tolerance of the Healthy Subject.*

1. *Individuals investigated.* Four individuals, three of whom were residents in the hospital, and one the biochemist, were tested, in one case six observations being made. The kidneys were considered blameless in all cases, though in none was the previous history free from infections.

The general effects of the dose of urea were not marked. No ill effects were

experienced, either by the normal individuals or by the nephritic or even uraemic patients. Diuresis was not always present and never conspicuous. The results are recorded in the accompanying table (Table I).

2. *Commentary on results.* i. *The resting level of blood urea* was found to vary between 21 and 38 mg. per 100 c.c. in Case 2 on six occasions. In this case the level was estimated hourly for twenty-four hours (see Chart I) and found to fluctuate between 30 and 36 mg. in spite of meals. The times of the meals appeared to have little relation to the vacillations, the level of 36 being recorded three times—after breakfast, before and after lunch.

ii. *The rise in blood urea* varied considerably, being usually complete in 30 minutes, occasionally not till 60.

There is no apparent significance in the rate of rise; it is doubtless dependent on circumstances of absorption in the stomach and duodenum.

In 2*a* and 2*f* the stomach contents were examined for urea:

30 minutes after the dose, in *a*, a sample of gastric contents contained 7.5 per cent. urea.

45 minutes after, in *f*, a sample contained 4.1 per cent.

60 minutes after, in *a*, the whole contents, 25 c.c., showed 0.75 per cent.

100 minutes after, in *f*, the whole contents, 30 c.c., showed 0.5 per cent.

Thus it appears that urea is present in considerable quantity 30 minutes after the dose. It gradually diminishes till at 60 minutes very little is left.

A large dose of 25 grm. is apparently still being absorbed, perhaps 2 hours after, from the duodenum, because of the persistently high level of blood urea in the 25 grm. curves.

iii. *The maximum.* 50 mg. is the highest level found after the dose. Usually it is about 40 mg., depending on the initial level.

The actual increase averages 15 mg. for a 25 grm. dose, and 10 for a 15 grm. dose.

iv. *The fall.* This is variable, but in all cases complete recovery, allowing 6 mg. for hourly fluctuation, is attained in 2 hours for all 15 grm. doses save in 2*c*, where 3 hours is required.

The recovery in 25 grm. cases is only beginning at 3 or 4 hours, and is quite incomplete 5 hours after.

2*b* is curious in having a small quick rise, and complete recovery in 30 minutes.

v. *The effect of dose.* This is very considerable. The difference between the 15 grm. and the 25 grm. cases, especially in the matter of recovery, is so great that the 15 grm. dose is carefully adhered to in dealing with pathological cases. In children the dose must be carefully proportioned. It may be that better results are to be attained with a smaller dose. To ascertain this, a completely fresh series of normal and pathological cases would require investigation.

3. *Conclusions re normal tolerance.* The normal individual with healthy kidneys reacts as follows to a urea tolerance test with 15 grm. of urea: The resting level is normal. The rise is 5–15 mg. in 30–60 minutes. The recovery

TABLE I. *The Normal Cases.*

Case.	Sex.	Age.	Remarks.	Urea given in Grm.	Urea concentration Result. % of Urea and Volume of Urine shown 1 hr. after Urea.	Urea Tolerance.						
						Figures = mg. urea in 100 c.c. blood.						
						Time in Minutes relative to taking Urea.						
						Before Urea.	15 min. after.	30	60	120	180	300
1 H. E. A.	M.	35	—	15	—	30	35	40	38	34	32	—
2a G. D. R.	"	25	Stomach contents examined on this occasion	15	3.1 % 100 c.c.	30	37	38	40	34	33	—
2b	"	"	Blood from finger	15	—	38	43	36	37	—	—	—
2c	"	"	—	15	—	32	38	48	44	—	40	—
2d	"	"	—	25	—	34	40	50	50	—	—	—
2e	"	"	—	25	—	28	—	40	41	40	40	—
2f	"	"	Stomach contents examined	25	—	27	—	—	42	—	43	39
3 R. P. G.	"	24	—	15	—	31	46	44	39	—	—	—
4 G. F. B.	"	25	—	15	3.2 % 55 c.c.	26	—	39	40	32	29	—

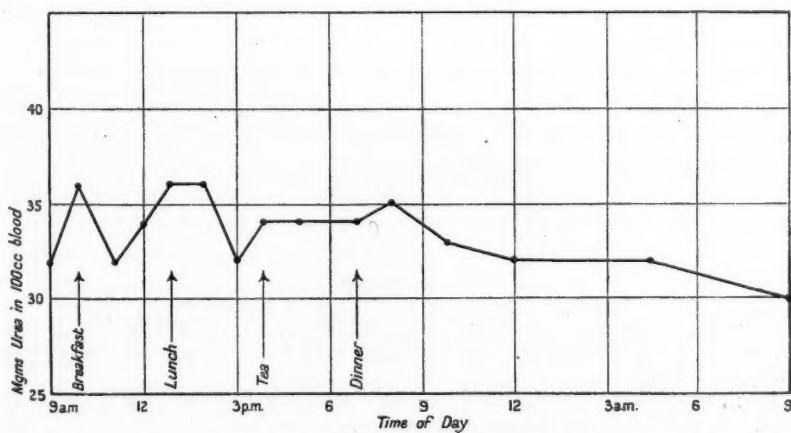


CHART I. Hourly levels of blood urea.

is complete in 120 minutes. A typical curve (Case 4, G. F. B.) is shown in Chart II.

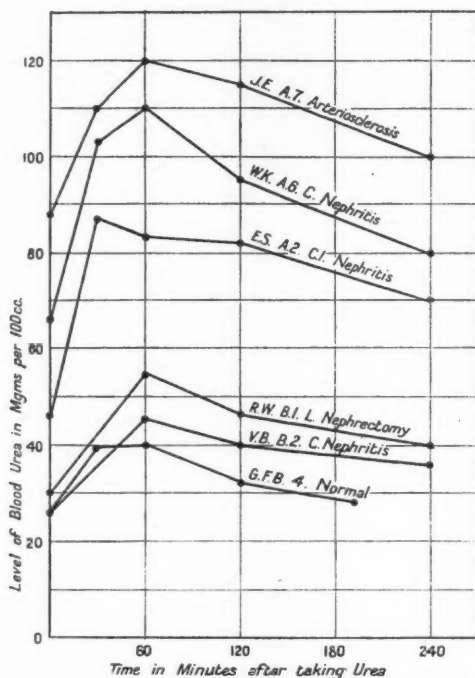


CHART II. Graphs showing urea tolerance. Dose 15 gm. in all cases.

#### *Urea Tolerance in Certain Pathological Cases.*

Twenty-four cases were examined, and the results are recorded for each one. The cases fall into two main groups.

The first (A cases), 8 in number, were grossly deficient in renal function.

The remaining 16 (B cases) were of a less definite character. Many were known to have had renal trouble. Others were investigated for renal mischief where symptoms and signs were vague.

The details of these cases are recorded in two groups, A and B (Tables II and III).

#### *The A Cases.*

A 1: was examined 2 months before his death. The level of blood urea was a great deal above normal. An enormous rise was followed by incomplete recovery in 4 hours.

A 2: was similar to A 1, save that the resting level was only a little above normal. A great rise was followed by incomplete recovery.

A 3: showed a normal resting level. The rise was not great, but distinctly above normal. The recovery was incomplete.



A 4 a: showed grave deficiency. The resting level was high. The rise was great, and recovery incomplete. The concentration figures were normal.

A 4 b: was taken when the heart had recovered and the oedema and ascites had cleared up. The resting level was the lowest recorded in all the present observations. The rise was trivial and recovery complete. The concentration was definitely deficient. This case is difficult. If the kidneys are not permanently damaged, as we are inclined to think, the concentration results are misleading in b. They are equally misleading in a, for then there must undoubtedly have been temporary renal inefficiency, possibly due to congestion of the kidneys, though high levels for blood urea are rare in simple cardiac failure. Truth in this case would not perhaps be reached without examination of the kidneys.

A 5 a: showed a slightly excessive rise starting from a normal level. Recovery was definitely poor.

A 5 b: one month later, when the patient seemed in the same state clinically, the resting level was found to be high. The rise was normal, but recovery poor as before. The concentration was the same.

A 6: the resting level was high: rise very great: recovery incomplete, but not poor.

A 7: the resting level was high: rise great: recovery incomplete, but not poor. The concentration was very poor, and the grave outlook given was proved correct by the death of the patient 3 days after operation.

A 8: the resting level was high for a boy of 5 years. The rise was enormous; no recovery in four hours. The dose of  $7\frac{1}{2}$  grm. was perhaps proportionally too large, and so obscured the result. The concentration was very poor.

Half of these cases, A 1, A 2, A 5, A 6, A 7, were so obviously deficient in renal function that biochemical estimations were not necessary. Out of the nine occasions when deficient kidneys were examined, the resting blood urea was within normal limits in 2 cases, slightly above in 2, and definitely above in 5. The concentration test gave normal figures in 1 case and definitely deficient ones in 8. The tolerance test revealed deficiency in all cases. Inasmuch, however, as definite evidence of renal inefficiency was gained by taking the resting level of blood urea in conjunction with the concentration, the *tolerance test was superfluous in all the A cases.*

#### *The B Cases.*

*Sub-Group (a):* 1 case: B 1.

This case had l. nephrectomy for tuberculous disease. The r. kidney was believed healthy.

This showed a normal resting level, a slightly excessive rise, a fair though incomplete recovery.

This patient is considered renally deficient, although he concentrates well.

*Sub-Group (b):* 3 cases: B 2, B 3, B 4.

These cases were young mild chronic nephritics.

B 2: showed a normal resting level, normal rise, but definitely poor recovery.

B 3: showed normal resting level, normal rise, but very definitely poor recovery.

B 4: showed normal resting level, normal rise, but poor recovery.

These three cases are considered to show definite renal deficiency, though the concentration tests are all good, and resting blood urea levels normal. In B 2 the cause of the renal affection was not known, but it was definitely established in B 3 and B 4.

*Sub-Group (c): 3 cases: B 5, B 6, B 7.*

These cases were known to have had acute nephritis previously, but were very well when examined.

B 5: showed normal resting level, normal rise, but definitely poor recovery. In view of this, and the findings at operation, this patient is considered deficient, in spite of the excellent concentration figures.

B 6: showed normal resting level, normal rise, but incomplete recovery.

In spite of the history and the concentration results, this patient seems to be functioning fairly well. He has no symptoms and is at ordinary work.

B 7: showed normal resting level, normal rise, and practically complete recovery.

This patient appears to function normally, being an exceptionally fit and energetic man.

*Sub-Group (d): 2 cases: B 8, B 9.*

These cases were examined within two months of onset of acute nephritis.

B 8: showed normal resting level, normal rise, but very definitely poor recovery.

Considered to be deficient.

B 9: showed resting level to be a trifle high, rise somewhat excessive, and recovery very definitely poor. The dose of urea in this case was proportionately high.

These kidneys are considered deficient. The concentration figures were better in the acute stage with a blood urea of 79 mg. than at this stage.

*Sub-Group (e): 3 cases: B 10, B 11, B 12.*

These cases were cardiac cases with some renal involvement

B 10: showed normal level, normal rise, definitely poor recovery. Is considered mildly deficient.

B 11 a: showed normal level, normal rise, poor recovery.

B 11 b: showed the same curve on a higher plane. The concentration is a little better than in a. These kidneys would appear slightly deficient. The superimposed cardiac failure made little difference to the renal efficiency. Compare A 4 a and b.

The improved concentration in b perhaps depends on the generally higher level of blood urea, though why this level should be higher is not clear.

B 12: showed normal resting level, normal rise, incomplete recovery.

This case is considered mildly deficient.

*Sub-Group (f): 2 cases: B 13, B 14.*

These cases were found to have some renal deficiency alongside their main complaint.

B 13: showed normal resting level, slightly excessive rise, quite definitely poor recovery.

These kidneys would appear deficient, in spite of the state of the urine and the concentration figures. The B.P. was 175, the hyperthyroidism having been present 5 years.

B 14: showed normal resting level, excessive rise, poor recovery.

This case is considered deficient.

*Sub-Group (g): 2 cases: B 15, B 16.*

These cases were suspected of renal disease, but found to have none.

B 15: normal resting level, normal rise, practically complete recovery.

These kidneys are considered normal.

B 16: showed normal level, normal rise, and complete recovery.

This case is considered normal.

For one reason or another, 12 out of the 16 B cases were known to have, or have had, some interference with the kidneys, which was conceivably embarrassing their function when examined.

In these 12 cases (all save B 13-16) the resting blood-urea level was normal in every case; the concentration test was normal or good in every case save B 6, B 11, and possibly B 12; the tolerance test showed deficiency in all cases save B 7.

In the remaining 4 cases (B 13-16) the resting blood urea level was normal in every case; the concentration test was normal in every case; the tolerance test showed deficiency in B 13, B 14; normal results in B 15, B 16. In the two former there was little evidence of renal trouble, but the circumstances made such a contingency quite likely. In the two latter, circumstances rendered renal deficiency quite possible, but none was found.

#### *Urea Tolerance as an Index of Renal Function.*

There are unsatisfactory features about all the renal tests hitherto proposed. Many are simple to perform, but in none can implicit faith be placed upon the result. The present results of the urea tolerance test have appeared to be more helpful in arriving at a just conclusion regarding the value of a patient's kidneys than either the simple blood urea level or the concentration test. There are obscure features, of course, in the tolerance results, and they must always be taken in conjunction with other biochemical findings, and with the clinical condition.

Urea tolerance is merely a fresh line of approach—one further addition to the great cloud of witnesses which are gathering round the renal patient. Nevertheless, it is based on physiological principles. The fact that there is a more or less constant level of urea in the blood seems established. Inefficient kidneys may result in an increased blood urea, and this high level in the blood may assist, to a certain extent, in giving a higher concentration in the urine and so give a better urea concentration test result than might be expected. This effect of blood urea on urinary urea has been explained by de Wesselow (2). Kidneys damaged to a less extent seem to be able to manage well enough with a normal blood urea, but their powers are fully extended in so doing. An extra dose of urea pushes up the level more, and maintains a high level longer, than when the kidney is healthy and has a margin of reserve.

Nephritis varies, of course, in kind. One damaged kidney seems to have difficulty chiefly with salts and gives a clinical picture of oedema. The azotemic nephritic is poor in power to excrete nitrogenous waste.

Therefore it may rightly be argued that the urea tolerance test is aimed at, and will reveal only the azotemic type. Unfortunately there is no clearly defined case of salt-retention nephritis in this series. Inasmuch, however, as many nephritics combine oedema and azotemia, the tolerance test may be fairly expected to show deficiency in the majority of cases.

The characters of a deficient tolerance result (see Table III) are that the resting level of blood urea is often normal. The rise is excessive if it is greater than 15 points. The significance of the rate of rise is not known. Many deficient cases show a normal rise. The degree of recovery at four hours is observed. Deficiency is considered present if recovery is not complete, after allowing 5 or 6 points for fluctuation of the resting level. The recovery is the feature by which to assess the curve.

As to the value of the test. In gravely deficient cases the test is superfluous. In the more doubtful cases it showed deficiency in 11 out of 12 cases, which had some definite renal interference. The twelfth case seemed, by all other signs, symptoms, and tests, to have cleared up completely.

The concentration test revealed deficiency in two only of these and perhaps a third. The resting level of blood urea was normal in every case.

Therefore there seems definite reason to suppose that the tolerance test is more reliable than either of the other two. It detects renal deficiency, which is missed by the concentration test and the single estimation of blood urea. The chief disadvantage of the test is the rather long period over which specimens must be collected.

#### *Summary.*

The tolerance of the body for urea is defined in certain normal cases.

The tolerance is studied in 24 cases of definite or suspected renal mischief.

The tolerance test results are compared and correlated with those of other tests, with the clinical condition, and with the operative or post-mortem findings when present.

The value and disadvantages of urea tolerance as an index of renal efficiency are discussed.

We have to thank Dr. Burnford, under whose care many of the patients were, for permission to do the work, and also Dr. Saunders, Dr. Burrell, Mr. Tyrrell Gray, Mr. Macdonald, and Mr. Simmonds for other cases. We tender our thanks also to Sister Kaye and Sister Healey, and to Miss Liddiard, in the laboratory, by whom the estimations were made with great care.

#### REFERENCES.

1. Twort and Archer, 'The Experimental Production of a Fatal Nephritis', *Lancet*, Lond., 1923, i. 1102.
2. de Wesselow, O. L. V., *The Chemistry of the Blood in Clinical Medicine*, Lond., 1924.

TABLE II. *The 'A' Cases. Severe Renal Deficiency.*

Case.	Sex.	Age.	Disease.	Clinical Particulars.	Urine.	Urea given in Test.	Urea Tolerance.				Urea Concentration.			
							Figures = mg. Urea in 100 c.c. Blood.				Vol. of each spec. in stated.			
							Times in min. relative to taking Urea.				c.c.			
							Before.	30 min. after.	60 min. after.	120 min. after.	Before Urea.	60 min. after.	120 min. after.	180 min. after.
1. R. G.	M.	44	Chronic interstitial nephritis	Scarlet fever and nephritis at 4 years. Aetiology unknown: arteriosclerosis: B.P. over 200 mm.: albuminuric retinitis. Asthma: vomiting	Albumin, blood, casts	15	220	260	299	290	270	1-1	1-8	1-4
2. E. S.	F.	66	"	Loss of weight; sickness and constipation for 2 years. B.P. 270 mm.	Albumin, blood, hy. and g. casts, a little pus	"	46	87	83	82	70	1-2	1-3	—
3. C. A.	M.	62	Arterio-sclerosis	Weakness, dyspnoea, oedema, and polyuria from time to time. B.P. 110	Nil	"	33	38	54	52	45	0-9	1-4	1-3
4a. F. W.	"	49	Cardiac failure	Auricular fibrillation—Massive oedema—slight jaundice. B.P. not obtainable	Albumin, casts	"	170	213	236	217	212	2-1	2-1	2-1
4b.	"	"	"	4 weeks later: loss of all oedema, fibrillation, and jaundice. Patient not yet up. B.P. 115	Casts, blood (a little)	"	20	—	27	24	23	1-2	1-5	1-7
5a. A. C.	"	34	Subacute nephritis	Intractable albuminuria—oedema while up. B.P. 155. Duration 4 months	Albumin, casts, blood	"	40	48	59	60	55	1-3	1-5	1-5
												56	128	85
												57	142	43

Case 1. P.M.: Small red granular kidneys; heart + +; blood urea 250 days before death.





TABLE III. *The 'B' Cases.*

Case.	Sex.	Age.	Disease.	Clinical Particulars.	Urine.	Urea given in Test.	Urea Tolerance.					Urea Concentration.				
							Figures = mg. Urea in 100 c.c. Blood. Times in min. relative to taking Urea.					% of Urea in each spec. Vol. in c.c. of each spec. Urine				
						Gm.	Before.	30 min. after.	60 min. after.	120 min. after.	180 min. after.	Before.	30 min. after.	60 min. after.	120 min. after.	180 min. after.
1. R. W.	M.	51	Left nephrectomy	L. kidney excised for T.B. of 2 years' duration 10 days before test. R. kidney believed to be healthy	Trace albumin, no casts, a little pus, no T.B.	15	30	—	54	46	40	1.6 %	2.1	2.5	2.7	2.7
2. V. B.	"	19	Mild chronic nephritis	Headaches only, 5 weeks' duration. B.P. 145 mm.	Trace albumin, a few casts, R.B.C., and leucocytes	"	26	—	45	40	36	2.1	2.4	3.0	3.0	2.9
3. E. A.	"	10	"	Acute nephritis in 1918 after scarlatina. Chorea since. Nausea, giddiness, oedema of feet and eyes, headaches. B.P. 105. Nil in heart. Better after tonsillectomy	Trace albumin, no blood, no casts	10	31	39	40	46	42	3.0	3.9	3.2	5.6	8.2
4. R. B.	"	12	"	No acute nephritis: anaemia, headaches, malaise, puffy eyes. W.R. + ±. B.P. 110. Improvement. Concentration 6 weeks before averaged 1.3 %	Trace albumin, casts (a few)	"	28	34	43	42	36	1.2	2.2	2.4	2.4	2.4

TABLE III (continued).

Case.	Sex.	Age.	Disease.	Clinical Particulars.	Urine.	Urea given in Test.	Urea Tolerance.				Urea Concentration.			
							Figures=mg. Urea in 100 c.c. Blood. Times in minutes relative to taking Urea.				% of Urea in each spec. Vol. in c.c. of each spec. Urine			
							30 mins. after.	Before.	60	120	240	Before 30 mins. Urea.	120	180
5.	C. B.	M.	26	Previous acute nephritis	Nephritis a frigore 18 months before with albumin and blood—(a little), casts no oedema. B.P. 115. Present complaint gastric	15	26	39	44	40	37	3.6	4.0	4.1
												28	85	28
6.	C. J.	"	33	"	Acute nephritis 8 years ago—five months in hospital—massive oedema, ascites, casts—persistent albumin. Now well and at work	"	26	39	40	37	32	0.9	1.2	—
												165	180	80
7.	C. L.	"	"	"	Acute nephritis 2 years ago. Blood, albumin, casts. Blood urea 45 and 47. No symptoms whatever now	"	28	31	34	38	35	3.8	3.4	2.9
												15	51	71
8.	G. C.	"	31	Acute nephritis	Haematuria for 2 months, severe at onset. B.P. 145. Cause—chill or enlarged l. tonsil	"	30	40	40	43	40	2.0	2.2	3.0
												142	56	56
9.	J. M.	"	6	"	Tested 1 month after onset. Cured by tonsillectomy. Concentration at onset 2.1 %. Blood urea 79.	"	32	31	52	50	48	0.3	1.0	2.4
												42	85	68
														56

Case 5. At operation, kidneys found to be large and soft.

Case 8. Calculus in bladder-wall seen in X-ray. No symptoms.

TOLERANCE FOR UREA IN HEALTH AND DISEASE 287

10. A. S.	F.	32	Cardiac and mild chronic nephritis	Aching and swelling of feet, thirst, polyuria for 5 weeks. Anaemia. Improved rapidly. B.P. 120	Nil	"	28	43	45	40	36	2.9 113	2.9 71	3.1 41	3.5 100
11 a. B. B.	"	53	Cardiac failure and chronic nephritis	On admission: oedema, ascites, large liver. B.P. 225. Aortic and mitral murmurs	Albumin (a little), casts (a few)	"	30	32	46	40	37	0.7 438	0.9 227	1.3 57	1.6 113
11 b.	"	"	"	3 weeks later: great improvement clinically. B.P. 180. Normal diet	Albumin (a trace)	"	38	50	52	54	44	1.0 113	1.4 113	1.8 197	1.8 85
12. R. K.	"	34	Cardiac and mild chronic nephritis	Dyspnoea, palpitation, swelling of feet, in attacks. Tachycardia. B.P. 180.	Albumin (a little), casts (a few)	"	26	36	40	38	32	0.7 240	1.6 80	1.8 90	2.2 120
13. G. H.	"	33	Hyperthyroidism	No renal symptoms. Urea estimated in the blood taken for sugar tolerance. 5 years history. B.P. 175	Nil	"	31	51	52	54	49	12.3 113	2.7 56	2.7 85	2.8 85
14. L. O.	"	49	Cystitis	Vomiting, fainting, nervous. B.P. 160	Muco-pus, coliform B., blood (a little), no casts, no albumin	"	28	—	60	56	42	1.8 56	2.8 84	2.7 84	3.3 56
15. S. B.	"	26	Jaundice	At operation found to be due to hepatitis. Syphilis one year before. Laevulose test normal. B.P. 110	Bile, nil else	"	28	31	42	37	33	1.7 144	1.8 113	2.5 113	2.8 113
16. R. P.	"	45	Chronic bronchitis	Oedema of ankles at times. Heart: nil found. B.P. 140	Albumin (a little), no casts, pus; a few R.B.C. and leucocytes	"	34	38	40	36	31	2.7 85	2.1 35	2.3 85	2.8 28

## CALCIUM AND MAGNESIUM IN SOME PATHOLOGICAL SERA<sup>1</sup>

By ELSIE WATCHORN

(From the Biochemical Laboratory, Cambridge)

WHILE much work has been done on calcium in the blood, the magnesium has been almost entirely neglected. It has been stated frequently that the latter is of little importance and has no clinical significance, and although this is possible, it seemed desirable to investigate the subject a little, and to see, in the first place, what its variations are in normal and pathological conditions. It was considered worth while to estimate the calcium content of the serum at the same time, partly to determine any existing relation between the two, and partly because further details with regard to calcium are not without interest. The calcium will be considered first.

### *Calcium.*

Serum was used, and the method of Kramer and Tisdall (1) employed. This method has been found very satisfactory when once the worker has become accustomed to the correct end-point in the titration. Duplicates did not differ by more than 2 per cent., and generally by less than 1 per cent.

A series of eight normals gave values ranging from 10.00 to 10.80 mg. per cent. For the purpose of this paper the normal range will be taken as from 9.8 to 11.0 mg. per cent.

Thirty-seven cases were investigated, the patients either being under treatment in the Eye and Ear Infirmary, Liverpool, or ill enough to have consulted a specialist. Fourteen cases were normal, three showed a condition of hypocalcemia, and the remainder hypercalcemia.

The following are the details of the patients with reduced calcium:

(Letters are used to distinguish the various cases, sex is indicated, and age given when it is known.)

(K) m. 60.	Nephritis with pyrexia . . . .	9.22 mg. per cent.
(EE) m. 61.	Optic neuritis—no evidence of infection	9.68 " "
(Q) m.	Syphilis of long duration; Wassermann test remains positive in spite of pro- longed treatment . . . .	8.20 " "

<sup>1</sup> Received December 28, 1924.

# CALCIUM AND MAGNESIUM IN PATHOLOGICAL SERA 289

The cases of increased calcium have been divided into three groups, and for comparison placed side by side with the normals.

Normals.	mg. %.	11.0-12.0 mg. %.	mg. %.	12.0-13.0 mg. %.	mg. %.	Above 13.0 mg. %.	mg. %.
(A) m. 42. Dyspepsia with intestinal attacks. Much indican in urine . . . . .	10.59	(F) m. 48. Chronic catarrh, antral and tonsil infection . . . . .	11.23	(R) f. 48. Fibrositis for several years. Legs chiefly affected . . . . .	12.70	(M) m. Iritis—very bad post-nasal infection . . . . .	13.22
(C) f. 35. Duodenal ulcer and cholecystitis . . . . .	9.82	(H) f. 30. Antral and ethmoidal disease . . . . .	11.23	(W) f. 53. Chronic rheumatoid arthritis and antral infection . . . . .	12.11	(Z) m. 61. Early fibrositis—history of gonorrhoea 40 years ago . . . . .	14.29
(D) m. 39. Tubercular keratitis, severe . . . . .	10.34	(T) f. 36. Disseminated sclerosis, recently developed . . . . .	11.70	(DD) f. 13. Chronic iritis, very bad post-nasal and sinus infection . . . . .	12.21	(CC) f. 18. Chronic iritis with severe post - nasal and sinus infection . . . . .	13.87
(E) f. 45. Syphilitic iritis, recent infection . . . . .	9.86	(NN) m. 39. Disseminated sclerosis, no definite findings . . . . .	11.32	(Y) m. 48. Syphilitic iritis. Wassermann now negative, previously positive . . . . .	12.25		
(G) m. 45. Simple anaemia, slight. Other blood and urine findings normal . . . . .	10.50	(N) m. Syphilitic iritis, recent . . . . .	11.82	(P) m. Syphilis, fairly recent. Wassermann positive . . . . .	12.46		
(L) f. 46. Giant urticaria, chronic . . . . .	10.30	(FF) m. 42. Chronic iritis, with intestinal infection . . . . .	11.78	(KK) m. 42. Gonorrhoea 1905—relapsed 1919. Severe infection . . . . .	12.00		
(S) m. 65. Chronic diarrhoea, and thyroid enlargement . . . . .	10.94	(RR) f. 55. Facial paralysis of 7 years' duration. Numbness of hands and feet. No syphilis . . . . .	11.40	(MM) m. 44. Old kidney trouble—suggested dropped kidney. Chronic post-nasal catarrh . . . . .	12.40		
(U) f. 66. Advanced rheumatoid arthritis . . . . .	10.68	(PP) m. 31. Gonorrhoea contracted 1911. Never treated—gonococci still present in urine and urethral smear . . . . .	11.72				
(X) m. 51. Synovitis of long duration . . . . .	10.44	(OO) m. 55. Fibrositis, fairly recent development . . . . .	11.72				
(BB) m. 44. Acute 'indigestion'; sugar tolerance poor . . . . .	10.40	(HH) m. 38. Old duodenal ulcer—patient been on calcium and parathyroid treatment . . . . .	11.03				
(GG) m. 6. Chronic eczema . . . . .	10.02						
(JJ) m. 42. Mild nephritis, recent . . . . .	10.98						
(QQ) m. 38. Chronic catarrh, very slight. Otherwise in very good health . . . . .	10.78						
(R) m. Chronic iritis, —very little evidence of cause . . . . .	10.98						

It has been stated by various workers, more particularly by Jansen (2), that the calcium content of serum is more frequently decreased than increased in pathological cases. The results reported in the present paper apparently contradict this, but this is probably due to the type of case which happened to be available for investigation. It will be noticed that of the patients with increased serum calcium many had some old catarrhal infection of post-nares, sinus, or tonsil. In the writer's experience, extending over a large number of calcium estimations, one of the most notable facts is the frequency with which the calcium in the serum seems to be increased in such conditions. Even if the

normal limit of variation is extended to 12 mg. per 100 c.c., five out of seven of these cases must be considered as having abnormally high calcium contents. On the other hand, in the cases of fibrositic rheumatism here reported, though the calcium was increased, it did not reach the figures given by some workers, although they were all severe cases (even those of recent development), and some probably gouty. Weil and Guillaumin (3) give figures ranging from 14 to 17.8 mg. per cent. in similar cases, while Coates and Raiment (4) have recently reported still higher figures in undoubted cases of gout. Only one case of syphilitic infection was normal (a recent infection), although Halversen, Mohler, and Bergeim (5) obtained normal values in all their cases. The two cases of skin disease (L and GG) were normal, and this appears to be the usual finding (6).

As evidence that increased calcium in the serum is not necessarily the result of long-standing infection, but may occur quickly, an experience of my own may be quoted. On May 23 my serum calcium was normal (10.39 mg. per cent.), but on June 3 my arm was bitten by a fly and rapidly became very septic. On June 9 my serum calcium had risen to 12.02 mg. per cent., and continued between this figure and 11.89 mg. per cent. until the end of October, when it stood at 11.49 mg. per cent. The septic arm was followed by much pain in the elbow and shoulder, spreading up the neck and into the eyes. A species of crisis developed, with pain and stiffness in all the limbs, a slight rise of temperature ( $100.2^{\circ}\text{F.}$ ), and frequent cramps, especially in the hands. The symptoms gradually passed off, and had practically disappeared when the figure of 11.49 mg. per cent. was obtained. At the beginning of December symptoms had entirely disappeared, and the serum calcium was then 10.98 mg. per cent., i. e. still in the higher limits for a normal person.

### *Magnesium.*

The method used was based on that of Hammett and Adams (7), but several modifications were made. The accuracy of the method was tested by working on known solutions, and whenever possible duplicate determinations were made. Blood was in all cases drawn from an arm vein and allowed to clot at room temperature.

*Normals.* A series of normals investigated by Briggs gave figures from 2.23 to 2.50 mg. per cent. In a series of normal determinations made during the present work similar results were obtained, as the following figures show :

Women	2.34 mg. per cent.	Men	2.50 mg. per cent.
	2.33 " "	2.34 " "	
	2.47 " "	2.30 " "	
		2.46 " "	
		2.27 " "	
		{ 2.08 " "	
		{ 2.45 " "	



# CALCIUM AND MAGNESIUM IN PATHOLOGICAL SERA 291

Normal.	mg. %	Up to 12.0 mg. % Increase.	mg. %	12.25 mg. % Increase.	mg. %	25.0-31.0 mg. % Increase.	mg. %
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## Cases with Decreased Calcium.

(EE) m. 61. Optic neuritis . . . . .	2.85	(K) m. 60. Nephritis and pyrexia . . . . .	3.58
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## Cases with Normal Serum Calcium.

(A) m. 42. Dyspepsia recent . . . . .	2.88	(C) f. 35. Duodenal ulcer and cholecystitis . . . . .	2.86	(X) m. 51. Synovitis . . . . .	3.03	(B) m. Chronic iritis—cause undetermined . . . . .	3.48
(R) f. 45. Syphilitic iritis . . . . .	2.53	(S) m. 65. Chronic diarrhoea . . . . .	2.82	(QQ) m. 38. Slight catarrh . . . . .	2.99		
(G) m. 45. Simple anaemia . . . . .	2.49	(PB) m. 44. Acute 'indigestion' . . . . .	2.76				
(L) f. 46. Giant urticaria . . . . .	2.50	(GG) m. 6. Chronic eczema . . . . .	2.75				

## Cases with Calcium of 11.0-12.0 mg. %.

(F) m. 48. Chronic catarrh, &c. . . . .	2.77	(T) f. 36. Disseminated sclerosis . . . . .	3.09	(H) f. 30. Antral and ethmoidal disease . . . . .	3.33
(N) m. Recentsyphilitic iritis . . . . .	2.86	(HH) m. 38. Duodenal ulcer . . . . .	3.22		
(FF) m. 42. Chronic iritis . . . . .	2.89	(OO) m. 55. Recent fibrositis . . . . .	2.97		
(NN) m. 39. (?) Disseminated sclerosis . . . . .	2.85				
(RR) f. 55. Facial paralysis . . . . .	2.85				

## Cases with Calcium of 12.0-13.0 mg. %.

(DD) f. 13. Chronic iritis with post-nasal infection, &c. . . . .	2.59	(R) f. 48. Fibrositis . . . . .	2.87	(Y) m. 48. Syphilitic iritis . . . . .	3.36
(MM) f. 44. Old kidney trouble and catarrh . . . . .	2.58	(W) f. 53. Rheumatoid arthritis and antral infection . . . . .	2.85		
		(P) m. Recent syphilis . . . . .	2.86		
		(KK) m. 42. Old gonorrhoea . . . . .	2.90		

## Cases with Calcium above 13.0 mg. %.

(CC) f. 18. Iritis with sinus infection, &c. . . . .	2.74	(Z) m. 61. Fibrositis and history of gonorrhoea . . . . .	3.21
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A curious result was obtained in the last male case on p. 290. On the first occasion the subject showed a considerable degree of nervousness. As he had been asked to volunteer about 3¼ hours before he was actually bled, it was thought that this period of nervousness might have been long enough to have affected the magnesium content of his blood (calcium was not estimated), especially as there was no other reason to account for so low a figure. A fortnight later blood was again taken as rapidly as possible after obtaining permission, and gave a quite normal result. While it is not desirable to lay too much stress on this observa-

tion, it would seem that the possible effect of nervousness, especially when existing over a period of several hours, must be borne in mind.

To test the range of variation in a normal individual, J. B. S. H. was bled on several occasions extending over a period of five months, and gave the following figures (mg. per cent.): 2.42, 2.41, 2.41, 2.32, 2.46, 2.45. The same subject was on one occasion bled one hour and six hours after a meal, the magnesium content of the two samples being 2.40 and 2.33, respectively. This strongly suggests that not only is the content of magnesium very constant in normal human sera, but that it is also constant in each individual during health. The average figure can then be taken as 2.2-2.6 mg. per cent.

*Pathological cases.* Thirty-two cases were investigated, twelve being patients in the Eye and Ear Infirmary, Liverpool. Only seven fell within normal limits, the remainder having an increased magnesium content of the serum. In the preceding table the distinguishing letter or letters refer to cases already described under calcium, and in most cases an abbreviated description of the clinical details is used. The age and sex is, however, repeated for convenience. The cases are subdivided according to the calcium result.

In the case of my own septic arm, the magnesium was not estimated on the first occasion of the calcium determination, but a fortnight later was found increased to 2.98 mg. per cent. from the previous normal of 2.32. It remained between this figure and 3.11 mg. per cent. until the beginning of December, when it was found to be strictly normal, i.e. 2.31 mg. per cent.

A raised magnesium content of serum has been found in rheumatism by Weil and Guillaumin (3), ranging from 2.7 to 3.3 mg. per cent., and Salvesen and Linder (8) sometimes found a reduction and sometimes an increase in nephritis, but magnesium does not seem to have been investigated in the other conditions mentioned in this paper.

In most cases it will be noticed that there was a condition of active bacterial or parasitic infection present, often of long duration. The patients were obviously in very poor health, though none of them was confined to bed.

It will be seen that there was no definite parallelism between the calcium and the magnesium.

#### *Summary.*

1. In some pathological conditions investigated, the calcium of the serum was found in most cases to be slightly increased.
2. The normal magnesium content of serum was found to be 2.2 to 2.5 mg. per cent., and to be very constant.
3. In nearly all the pathological conditions investigated, the serum magnesium was found to be increased, sometimes as much as 30 per cent., or more.
4. No definite relation between the variations in calcium and magnesium could be found.

My thanks are due to several people for help in various ways. To Dr. E. Cronin Lowe of Liverpool I am deeply indebted, for supplying me with blood from the pathological cases, and for so kindly allowing me to carry out part of the work in his private laboratory. It is a pleasure also to take this opportunity of expressing some part of the thanks I owe to Mr. J. B. S. Haldane for his constant help and encouragement, while I have also to thank Professor Hopkins for consenting to read and criticize this paper.

## REFERENCES.

1. Kramer and Tisdall, *Journ. Biol. Chem.*, Baltimore, 1921, *xlvi*. 475.
2. Jansen, *Deutsch. Archiv Klin. Med.*, Leipzig, 1924, *cxliv*. 14.
3. Weil and Guillaumin, *Compt. Rend. Soc. Biol.*, Paris, 1923, *lxxxviii*. 732.
4. Coates and Raiment, *Biochem. Journ.*, Camb., 1924, 921.
5. Halversen, Mohler, and Bergeim, *Journ. Biol. Chem.*, Baltimore, 1917, *xxxii*. 171.
6. Urbach and Simhandl, *Klin. Woch.*, Berlin, 1923, *ii*. 1600.
7. Hammett and Adams, *Journ. Biol. Chem.*, Baltimore, 1922, *lii*. 211, *liv*. 565.
8. Salvesen and Linder, *ibid.*, Baltimore, 1923-4, *lviii*. 617.

## THE RELATION OF INFECTION TO DIABETIC COMA<sup>1</sup>

By GEORGE GRAHAM

(From the Laboratory of the Medical Clinic, St. Bartholomew's Hospital)

It has long been recognized that patients with diabetes mellitus succumb very easily to other diseases, but the part played by other infections has become much more obvious since the introduction of insulin.

Campbell (1), as a result of the early work in Toronto, reported that out of 14 cases of coma, 7 died, and in 5 of these there was an associated condition which was sufficiently severe to result fatally apart from the diabetic condition. Joslin (2) reported 1 case of coma in which a pneumonia was discovered at autopsy. Williams (3) reported 9 cases of coma, and in 1 of these a septicaemia was present, secondary to a gangrene of the stump of an amputated leg. Frissell and Hajek (4) found an additional serious disease in 5 out of 6 cases of coma, pneumonia being present three times, carbuncle and German measles once each. Collier (5) reported 2 patients with coma in whom pneumonia was present. Both patients recovered after large doses of insulin. Rabinowitch (6) has also observed that the pancreatic function is deranged by infection.

In the majority of the cases reported, the nature of the complicating disease was diagnosed before death, but in the past patients often died in coma without any other disease being detected either in life or at autopsy. Formerly it was rare for a patient to recover consciousness, but now the great majority of patients do so, for a while at all events. It has, therefore, been possible to watch patients for some days who would almost certainly have died very shortly after admission to hospital unless insulin had been given. Under these conditions the signs of another disease usually became apparent.

Between March 1923 and May 1924 the writer saw seven patients who had been admitted to St. Bartholomew's Hospital either in coma or nearly in coma, and two others at the Royal Northern Hospital. In two no source of infection could be found; one of these became unconscious seven days after the onset of the thirst and polyuria, and it was assumed that the coma was directly due to the severity of the disease. Both these patients made good recoveries. The other seven cases may be described under the following headings:

### A. *Cases with an obvious infection.*

*Case I.* A man with a short history of diabetes in whom a swelling of the parotid appeared while he was undergoing the fasting treatment. He became

<sup>1</sup> Received October 6, 1924.

unconscious very suddenly and a large abscess of the parotid was found. This was opened and 30 units of insulin were given, but the man died four hours later. Very little insulin was available at that date.

*Case II.* A woman, aged 56, had had diabetes for some six years. She was admitted in coma and a large swelling of the knee-joint was found. Some turbid fluid was withdrawn which contained many polymorphonuclear leucocytes, but on culture was sterile. She recovered consciousness in eight hours after 60 units and made a good recovery.

*B. Cases with no obvious infection on admission, but in which a definite lesion would have been found at an autopsy if the patient had died in coma.*

*Case III.* A man, aged 21, had had diabetes for three years, but had not dieted carefully and had usually passed sugar. He was admitted in deep coma: blood-sugar 0.70 per cent.: unable to swallow: pyrexia. He recovered partial consciousness at end of 24 hours after 70 units of insulin, and complete consciousness in 36 hours after a further 70 units. The pyrexia persisted, but it was not until 14 days had elapsed that signs of disease were detected in the lungs and he began to expectorate. At autopsy, four weeks after the onset of the coma, a large cavity was found in each lung partly due to an active tuberculosis and partly to a gangrene of the lung.

*Case IV.* A girl, aged 16, had had diabetes for three years and had passed sugar all the time. She had a cataract in each eye, and was admitted almost in coma after a long railway journey. The signs of impending coma disappeared very quickly after 20 units of insulin. It was only after four weeks that it was recognized that she had either a big area of consolidation or a tuberculous cavity at the right base. She left hospital at her own request, taking 55 units of insulin a day. She reached home safely after a long railway journey, but died three days later. No autopsy was obtained.

*C. Cases with no signs of any other infection, and which would probably have shown no lesions of other diseases at an autopsy if the patient had died in coma, unless the examination had been very complete.*

*Case V.* A woman, aged 18, had had diabetes for  $1\frac{1}{2}$  years and had passed sugar for most of the time. She became unconscious during a mild epidemic of influenza. She recovered consciousness about 36 hours later, after 130 units of insulin. She had no pyrexia at this time, but it appeared in the course of the next week. It was then found that she had a purulent nasal discharge, which persisted for the next eight weeks with recurrent bouts of temperature. Sixty-six units of insulin were given, but this was not sufficient to keep the urine sugar-free. She was admitted into hospital and pus was found in the antrum of Highmore. This was drained, and she was discharged 12 weeks later, requiring only 25 units of insulin on the same diet as before admission of 1,400 calories and 16 gm. of sugar. The blood-sugar was normal in the morning, before insulin, on this dose.

*Case VI.* A woman, aged 20, had had thirst and polyuria for three months, but the diagnosis of diabetes had not been made as she had not consulted a doctor. She had been ailing and unable to go to work for three days before admission and became unconscious rather suddenly in the night. She recovered consciousness six hours after a dose of 40 units of insulin. No definite signs of

disease could be found, and, although the pulse-rate was 120 on admission, the temperature was only 95° F. The next day the temperature rose to 99° F. and remained at this level for the next two days. The pulse-rate fell to normal on the ninth day after admission. There was a great deal of influenza about at the time and it was suspected that she had this disease.

*Case VII.* A man, aged 31. He had had diabetes for the last three years and had been dieted to a certain extent, but had not kept closely to a starch-free diet and had passed sugar most of the time. Since he was alive three years after the onset of the disease, it is probable that the original attack was not very severe. On June 5, 1923, he felt unwell and vomited in the evening. He was seen by a doctor who did not discover any signs of disease apart from the glycosuria. He was found the next morning completely unconscious and was admitted to St. Bartholomew's Hospital at 1 p.m. Condition on admission: A well-developed man, not wasted. Completely unconscious, but able to swallow. Temperature 95° F.: pulse very feeble, rate 120. The eyeball tension was very low, and there was well-marked lipaemia retinalis. The blood-plasma was creamy white in colour. Air hunger was well marked, and the abdominal movements were very obvious. The percentage of carbon dioxide in the alveolar air was 0.9 per cent. The blood-sugar was 0.39 per cent. The urine contained much sugar and much aceto-acetic acid.

Immediately after admission 20 units of insulin were given, and as soon as the blood-sugar determination had been made, another 10 units. As he could swallow, 10 oz. of water were given each half-hour, and 1 oz. of castor oil was given with the first drink. At first he drank easily, but within two hours he showed some signs of returning consciousness and became difficult to nurse. Three hours after the first dose of insulin the blood-sugar had fallen to 0.31 per cent., but after six hours it had risen again to 0.34 per cent. By this time the man had become quite conscious and the eyeball tension had become normal. Another 20 units of insulin were given, and ten hours after admission the blood-sugar had fallen to 0.29 per cent. Since the blood-sugar was still so high, in spite of the 50 units in ten hours, it was realized that large doses of insulin would be required and 30 units were given at midnight. On the second day the general condition was greatly improved, but the pulse-rate was still 120 and the temperature had risen to 99°. The blood-sugar had fallen to 0.22 per cent. at 10 a.m., and at 3 p.m. was still at 0.21 per cent., but at 9 p.m., although 10 units had been given at 6 p.m., it had risen to 0.28 per cent. Another 30 units of insulin were given at 11 p.m. During the first day water only had been given, and in the second day only tea, coffee, and meat essence. On the third day the general condition as regards temperature and pulse was unaltered, but he had passed a bad night, and had a certain amount of discomfort in the right mastoid region. It was realized also that he was not quite so well, since the blood-sugar was 0.39 per cent. There did not seem to be any real tenderness of the mastoid region and the drum was not inspected. During the day, after 50 units of insulin, the blood-sugar was 0.28 per cent., and a further 20 units were then given, and another 10 units at 7 p.m. The blood-sugar fell to 0.25 per cent. at 10 p.m., and another 30 units of insulin were given. Since he was not sleeping, and the possibility of an infection had been considered, the ear was examined more carefully that night. The mastoid was definitely tender, but there was no oedema over it.

The membrana tympani was examined by Mr. Capps, the aural house surgeon, and was seen to be red and bulging. It was, therefore, incised under gas and oxygen and a small amount of pus escaped. Some food was given this day; total caloric value 500, protein 35 grm., fat 30 grm., and sugar 16 grm.. The fat was kept very low as the lipaemia was still very well marked. On the fourth day the general condition was better: the blood-sugar was 0.25 per cent., and although 80 units of insulin were given between 7 a.m. and 12 noon each



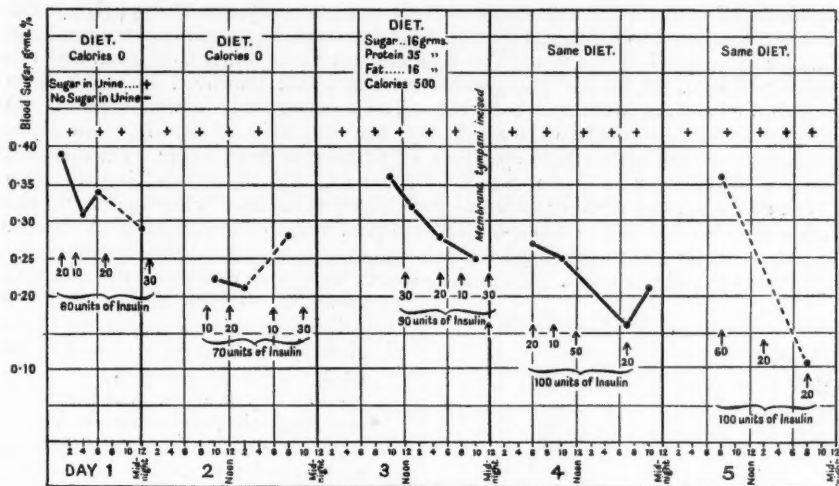


CHART 1.

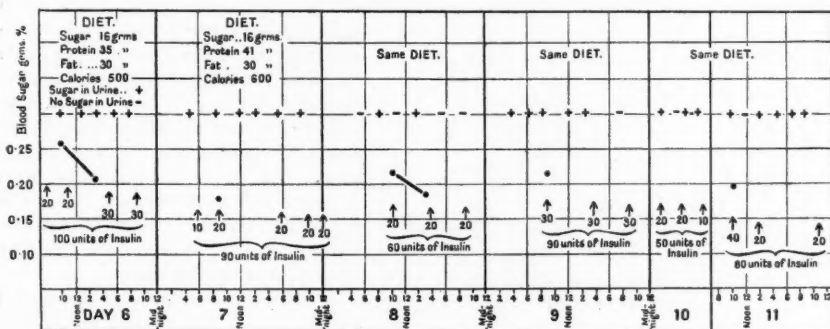


CHART 2.

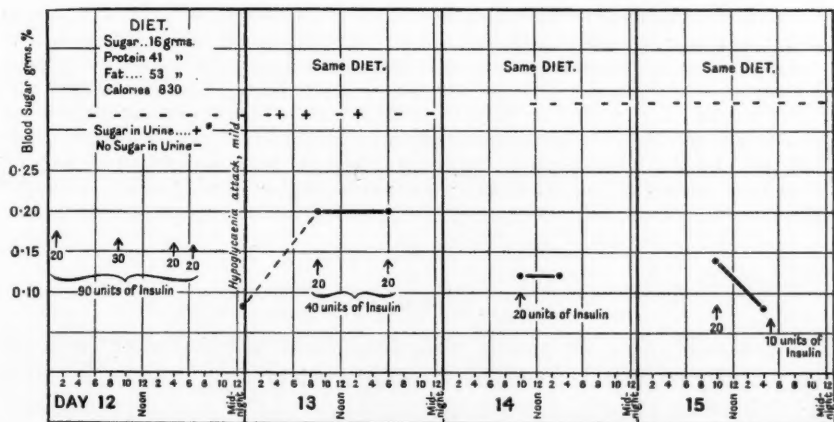


CHART 3.

specimen of urine contained sugar and there were no symptoms of hypoglycaemia. The ear continued to discharge for the next ten days, but recovered without any further operative interference. The temperature came down to normal and the pulse-rate also. Although the general condition had improved so much, large amounts of insulin were still required. The amount of food was kept at 500 calories from the fourth to the sixth day, but 100 units of insulin were given without ever making a single specimen of urine free from sugar. On the fifth day the blood-sugar at 7 a.m. was 0.36 per cent., and 60 units of insulin were given at 9 a.m., and another 20 units were given at 12 noon without making the urine sugar-free, and the blood-sugar at 8 p.m. was 0.155 per cent. Although the blood-sugar was at this level the urine passed in approximately three-hourly specimens contained sugar. From the seventh to the eleventh day the diet was

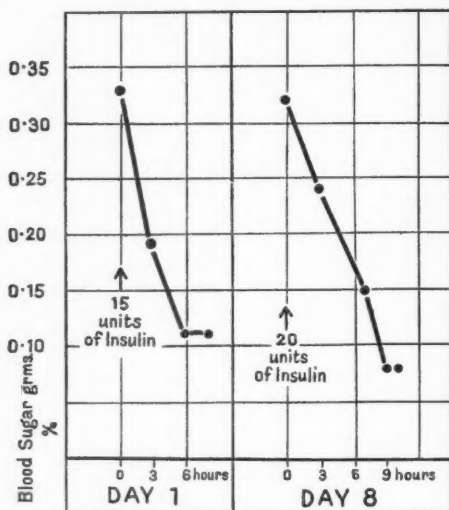


CHART 4.

increased to 600 calories, and the urine began to be sugar-free occasionally. The insulin dose was 60 or 90 units in the day. On the twelfth day the diet was increased to 830 calories, as the urine had been sugar-free most of the previous day, and 70 units of insulin were given. At 11 p.m. he complained of hunger pains and was excited, asking for extra food. An egg and a tomato relieved his symptoms. The blood-sugar at this time was 0.08 per cent. On the fourteenth day the blood-sugar at 9 a.m., and at 3 p.m., was only 0.12 per cent., although only 30 units of insulin were given in the day. The man is alive and well 1 year and 9 months later, but needs 36 units of insulin to maintain the fasting value of the blood-sugar within normal limits.

In the other cases in which an infection was discovered very large

doses of insulin were also necessary in the early stages, but as soon as they recovered the dose of insulin was reduced as in this case.

As a contrast to Case VII the figures for the blood-sugar are given (Chart 4) for one of the cases in which no signs of any other disease could be detected. The man was not quite unconscious, but air hunger was well marked and the percentage of carbon dioxide in the alveolar air was 0.8 per cent. The blood-sugar was 0.33 per cent., and a dose of only 15 units lowered the blood-sugar to 0.11 per cent. in six hours. The general condition improved in a most striking manner. Nine days later the blood-sugar was again at 0.32 per cent., and seven hours after 20 units of insulin it had fallen to 0.15 per cent., and after nine hours to 0.08 per cent.

#### Discussion.

In each of the seven cases of coma described an infection was present and was probably responsible for sending the patients into coma. Most of them had had diabetes for some years, and their condition, so far as could be ascertained, had never been serious. Five became comatose before there were any signs of

the infection, but in two the infection was easily recognized, for it involved the parotid gland in the one and the knee-joint in the other.

The way in which the infection acts cannot yet be decided, but there are at least three possible hypotheses:

1. The infection may have a direct effect on the  $\beta$  cells of the islands of Langerhans, which prevents them from producing enough insulin to avert coma. Against this hypothesis as the sole cause is the observation that the amount of insulin required to lower the blood-sugar of the comatose patients in whom an infection was present was much greater than that required for the patient in whom no infection was ever detected.

2. The infection may cause an increased demand for insulin because of the increase in the metabolism. Coleman and Dubois (7) found that there was an increase of approximately 40 per cent. in the basal metabolism of patients in the third week of a typhoid fever. This increase in the metabolism would presumably entail the production of more insulin, but at present it is impossible to say how much more.

3. The infection may destroy the insulin or form a substance which prevents it from acting properly. The large amounts of insulin which were required to lower the blood-sugar suggest that the insulin is less potent than usual, but there is no direct evidence in favour of the hypothesis.

The treatment of these cases requires little comment. The dose of insulin must be adequate, and to decide this point it is essential to estimate the blood-sugar at least once in the day and to test the urine for sugar every two or three hours.

#### Conclusions.

1. A general or local bacterial infection is often the direct cause of the onset of coma in a patient who has diabetes mellitus.

2. In the presence of such an infection insulin is much less effective in lowering the blood-sugar.

I have to thank Professor F. R. Fraser, Dr. H. Morley Fletcher, Dr. J. H. Drysdale, and Dr. W. Langdon Brown, for permission to quote their cases; Dr. C. F. Harris and Dr. V. R. Woodhill, for their assistance with the blood-sugar estimation; and the Ward Sisters, especially Miss M. Powell, Miss V. Etches, and Miss G. Evans, for much assistance in watching the patients.

#### REFERENCES.

1. Campbell, W. R., *Journ. Metabolic Res.*, Morristown, New Jersey, 1922, ii. 605.
2. Joslin, E. P., *ibid.*, Morristown, New Jersey, 1922, ii. 651.
3. Williams, J. R., *ibid.*, Morristown, New Jersey, 1922, ii. 729.
4. Frissell, L. F., and Hajak, J., *Arch. Int. Med.*, Chicago, 1924, xxxiii. 230.
5. Collier, W. T., *Lancet*, Lond., 1924, ii. 575.
6. Rabinowitch, J. M., *Canadian Med. Assoc. Journ.*, Montreal, 1924, xiv. 481.
7. Coleman, W., and Dubois, E. F., *Arch. Int. Med.*, Chicago, 1914, xiv. 168.

## THE SPINAL FLUID SUGAR IN ENCEPHALITIS<sup>1</sup>

By JAMES L. HALLIDAY

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### *Introduction.*

DURING the epidemic of encephalitis occurring in Glasgow between the months of March and July of 1924, an investigation was made on the sugar content of the spinal fluid. Many writers have found a high sugar content in the spinal fluid from encephalitis, and this increase they considered a useful aid in diagnosis. However, on surveying the literature, the evidence for an increase of the sugar content is not very convincing. Also the work, with one exception, is open to the criticism that the time relationship between the intake of food and the withdrawal of the spinal fluid is not stated. (See Bibliography.)

In this instance a series (I) of spinal fluids from cases of encephalitis taken after twelve hours' starvation gave a sugar content which corresponded with the figures obtained from a controlled series (II) of cases with no disease of the nervous system. In addition, a series (III) of spinal fluids from cases of encephalitis taken  $2\frac{1}{2}$  to 3 hours after the administration of 50 gm. of glucose or its equivalent in children gave a higher average reading than the average in Series I. This increase seemed to point to the existence of a spinal fluid sugar curve, and by withdrawing at the same time half-hourly specimens of blood and spinal fluid in three patients after the administration of glucose, the existence of such a curve was definitely demonstrated (Series IV).

### *Estimations in Spinal Fluid Sugar.*

The estimations were carried out in the laboratory of the City Fever Hospital, Ruchill, Glasgow. MacLean's method of estimation was employed. Unless otherwise stated all lumbar punctures were performed under a local anaesthetic. No adrenalin was used.

*Series I, in which 25 specimens of blood and spinal fluid, mostly from cases of encephalitis, were estimated for their sugar content, the specimens being taken simultaneously after 12 hours' fasting.* (See Table I.) The blood-sugar content varied from 0.068 per cent. to 0.128 per cent., the average being 0.095

<sup>1</sup> Received February 7, 1925.

per cent. These figures correspond with those (0.08-0.12) given by Maclean as normal for the fasting level in a healthy person.

The sugar content of the spinal fluid ran from 0.042 per cent. to 0.070 per cent., and the mean was 0.056 per cent.

The relationship expressed as a percentage between the sugar content of the fluid and the blood at fasting level varied from 49 to 70, and the average was 59.

TABLE I. *The Samples of Blood and Spinal Fluid were taken simultaneously after 12 hours' starvation.*

No.	Patient.	Sex.	Age.	Day of Illness.	Diagnosis.	Blood Sugar. %.	Spinal Fluid.			Fluid Sugar Blood Sugar $\times 100$ .
							Sugar. %.	Cell Count.	Globulin.	
1	E. G.	F	31	10	L. E.	0.128	0.070	10	+ (slight)	54
2	E. McP.	F	36	3	L. E.	0.123	0.060	30	—	49
3	M. F.	F	12	28	L. E.	0.109	0.061	5	+	56
4	J. B.	M	36	4	L. E.	0.109	0.056	60	+	51
5	A. D.	M	4	—	No apparent disease	0.109	0.053	5	—	49
6	M. McL.	F	8	12	L. E.	0.108	0.060	5	—	56
7	A. M.	F	15	15	L. E.	0.106	0.055	20	—	52
8	J. F.	M	48	14	L. E.	0.104	0.055	10	—	53
9	J. D.	M	47	27	L. E.	0.100	0.053	5	—	53
10	E. F.	F	2	—	No apparent disease	0.099	0.059	5	—	60
11	D. K.	M	15	13	L. E.	0.098	0.056	5	—	57
12	J. A.	M	16	13	L. E.	0.095	0.058	20	+ (slight)	61
13	J. R.*	M	51	8	L. E.	0.091	0.060	20	+	66
14	A. S.*	F	20	17	L. E.	0.089	0.052	50	—	58
15	M. H.	F	7	13	L. E.	0.089	0.052	15	—	58
16	M. McS.	F	30	33	Cystitis	0.089	0.051	5	—	57
17	M. A.	F	25	12	L. E.	0.087	0.059	50	—	68
18	A. McQ.	F	8	16	L. E.	0.086	0.059	40	—	69
19	J. M.	M	20	5	L. E.	0.085	0.058	90	—	68
20	S. A.	M	2	4	L. E.	0.083	0.055	310	+	66
21	W. D.	M	8	12	Intestinal toxæmia	0.082	0.058	5	—	70
22	J. McD.	M	38	4	L. E.	0.081	0.054	30	—	67
23	J. C.	M	25	24	L. E.	0.078	0.052	5	+	67
24	M. D.	M	14	20	L. E.	0.072	0.044	10	—	60
25	D. V.	M	9	29	L. E. ?	0.068	0.042	5	—	62
Average						0.095	0.056			59

\* These cases were lumbar punctured under chloroform.

Unfortunately, no literature is available on the normal spinal fluid sugar estimated by MacLean's method.

*Series II, in which six samples of spinal fluid taken previous to spinal anaesthesia were estimated for sugar.* (See Table II.) None of these patients could be described as strictly normal. Together with the two cases incorporated from Table I they furnished the only controls available. The figures vary from 0.050 per cent. to 0.065 per cent., striking an average of 0.057 per cent. almost identical with that of 0.056 per cent. in Series I. Unfortunately, it was impossible to take simultaneous samples of blood for sugar estimation.

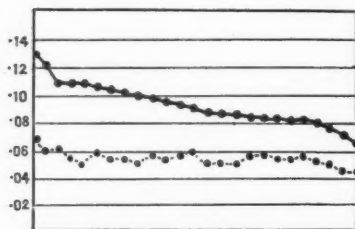
The absolute figures for normal spinal fluid obtained by other workers

using different methods cannot be compared with those quoted above, but the ratio between the blood- and fluid-sugar readings, no matter what the method used, are of value for comparison. In a series of normal individuals Seham and Nixon, using the Myers-Bailey method, found that the ratio between the fluid-sugar and the blood-sugar was on an average 56, with a minimum of 48 and a maximum of 70. This result agrees closely with the limits of 49 and 70, and the average of 59 obtained in Series I.

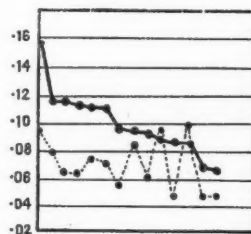
TABLE II.

No.	Patient.	Sex.	Age.	Diagnosis.	Spinal Fluid Sugar Content.	Time taken after Food.
1	M. B.	F	26	Uterine fibroids	0.054	12 hours
2	A. C.	M	68	Gangrene of leg	0.062	8 hours
3	L. H.	F	17	Appendicitis	0.061	9 hours
4	M. S.	F	35	Appendicitis	0.065	9 hours
5	J. M.	M	41	Gastric ulcer	0.050	7 hours
6	L. T.	F	29	Uterine fibroids	0.052	10 hours
From Table I {	A. D.	M	4	No apparent disease	0.053	12 hours
	E. S.	F	2	No apparent disease	0.059	12 hours

Average 0.057



GRAPH I, derived from Table I, showing the sugar content of corresponding specimens of blood and spinal fluid taken simultaneously after 12 hours' fasting. The blood-sugar readings are arranged in descending numerical sequence, and the results are plotted as a graph.



GRAPH II derived from Table III, showing the blood-sugar content at fasting level, and the corresponding spinal fluid sugar content several hours after the administration of glucose.

As the sugar ratios between the fluid and blood in encephalitis correspond with the normal ratio, and as the level of the blood-sugar in encephalitis is within normal limits, it does not therefore appear unjustifiable to conclude that the sugar content of the spinal fluid in cases of encephalitis is also within normal limits.

*Series III, in which an estimation was made of the sugar content of the blood after 12 hours' fasting, and of the spinal fluid 2 to 3 hours after the administration of glucose. (See Table III.)* In this series, chiefly of encephalitis cases, blood-sugar curves were made and lumbar puncture performed along with the withdrawal of the last blood specimen. The blood-sugar curves (not reproduced here) showed great variation. In the milder cases they were practically normal, but in the more severe cases they demonstrated a considerable defect in liver storage. Curves showing similar variations were found



in other infectious diseases, such as measles, diphtheria, phthisis, &c. It was concluded that no variety of blood-sugar curve was peculiar to encephalitis. This accords with the work of Olmsted and Gay (8), who pointed out the uncertain influence of toxæmia and infections on the nature and constancy of the blood-sugar curve. Similarly Schwab, in the case of nervous diseases, concluded that from the neurological standpoint it was impossible to attach characteristic types of curves to one type of disease.

TABLE III. *The Samples of Blood were taken after 12 hours' fasting; then glucose was administered, and the samples of fluid were taken 2-3 hours later.*

No.	Patient.	Sex.	Age.	Day of Illness.	Diagnosis.	Blood Sugar. %.	Spinal Fluid.			Fluid Blood. Sugar Ratio.
							Sugar. %.	Cell Count.	Globulin.	
1	M. B.	F	54	11	L. E. (died)	0.155	0.092	120	+	59
2	R. C.	F	31	9	L. E. (died)	0.117	0.078	110	+	67
3	J. W.	F	15	17	L. E.	0.117	0.064	60	-	55
4	M. A.	F	34	7	L. E.	0.115	0.062	50	-	54
5	E. M.	M	15	28	L. E.	0.113	0.073	30	-	65
6	J. M'G.	M	10	3	Intestinal toxæmia	0.111	0.074	5	-	67
7	M. H.	F	7	12	L. E.	0.111	0.069	30	-	62
8	J. S.	F	13	13	L. E.	0.096	0.055	5	-	57
9	R. M'K.	M	11	10	Rheumatic fever	0.095	0.083	-	-	87
10	E. C.	F	20	5	L. E.	0.093	0.060	90	+	64
11	J. A.	M	59	9	L. E.	0.087	0.093	50	-	107
12	M. A.	F	24	5	L. E.	0.087	0.049	-	-	56
13	W. M.	M	6	5	Intestinal toxæmia	0.085	0.099	-	-	106
14	M. D.	M	15	30	L. E.	0.070	0.047	-	-	67
15	W. T.	M	4	9	L. E.	0.067	0.049	50	-	73
Average						0.100	0.071			70

From a scrutiny of Table III, which is derived from the blood-sugar charts, it is seen that, in the fifteen cases in which lumbar puncture was performed at the end of the blood-sugar series, the average fasting level of the blood-sugar was 0.100 per cent., and the average level after glucose of the spinal fluid sugar was 0.071 per cent. Compared with the figures in Table I, the blood-sugar fasting level was merely 0.005 per cent. higher, but the average spinal fluid sugar level was 0.015 per cent. higher. The ratio between the fluid sugar and the blood-sugar was on an average 70, with a minimum of 54 and a maximum of 107; this ratio is higher than the ratio which obtained in Series I.

When the results in Tables I and III are plotted as graphs, it is seen that in Graph I the fluid-sugar readings are roughly parallel to the blood-sugar readings. In Graph II that relationship is distorted. Accordingly an investigation was made to determine the effect of the ingestion of glucose on the spinal fluid sugar.

*Series IV, in which contemporaneous sugar estimations of the blood and spinal fluid were made at intervals after the administration of glucose in three cases of encephalitis.* (See Charts I, II, III, and IV.) Lumbar puncture was done

immediately the first blood specimen was taken, and a sample of fluid was withdrawn. The lumbar-puncture needle and stylette were kept *in situ*. Fifty grm. of glucose were given. Samples of fluid were removed at half-hourly intervals by withdrawing the stylette, the first drops on each occasion being discarded. All the patients were lethargic and at first lay quiet; later they complained of being cramped in the back. When they complained the procedure was discontinued.

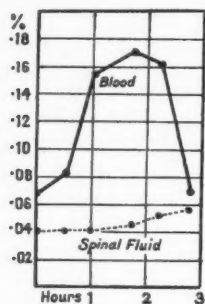


CHART I. Encephalitis. H. D., female, aged 30, fifth day. Slightly febrile; lethargic. Urine—before glucose: no sugar. 3 hours after glucose: benedict, green, opalescent. Fermentation negative.

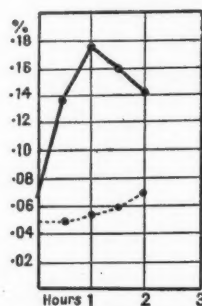


CHART II. Encephalitis. Mrs. I., aged 25, fifteenth day. Non-febrile; lethargic. 5 months pregnant. Urine—before glucose: benedict, green, turbid. 3 hours after glucose: benedict, yellow. Fermentation positive.

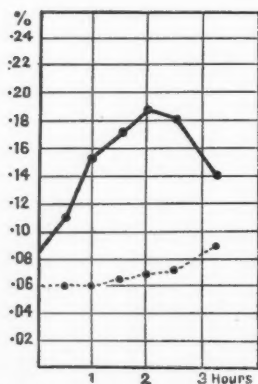


CHART III. Encephalitis. J. H., male, aged 28, sixteenth day. Febrile; lethargic. Urine—before glucose: benedict, clear green. 4 hours after glucose: benedict, greenish yellow, turbid. Fermentation positive.

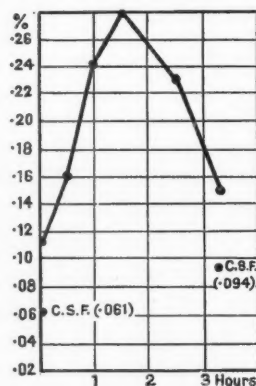


CHART IV. Encephalitis lethargica. E. M., female, aged 24, sixth day. Febrile; deeply lethargic. Enlarged thyroid gland. Urine—before glucose: benedict, clear green. 4 hours after glucose: benedict, yellow. Fermentation positive.

In the patient from which Chart IV was derived, only two lumbar punctures were made: one before the administration of glucose, the other along with the withdrawal of the last blood specimen.

*Chart I.* The blood-sugar curve shows delay in attaining its maximum, but the fall when it occurs is rapid. On plotting the spinal fluid sugar values, a

gradual rise begins after the first hour. It is noteworthy that the highest reading for the spinal fluid sugar was obtained when the blood-sugar had returned to fasting level. The second specimen of urine showed a slight reduction of Benedict's solution.

*Chart II.* Chart II from a pregnant woman shows a case of glycosuria perhaps renal in type. There is a rapid rise in the blood-sugar, and the spinal fluid sugar begins to increase after half an hour.

*Chart III.* The blood-sugar curve takes two hours to attain its maximum, and the fall, as far as is shown, is equally gradual. The appearance of an increase in the spinal fluid sugar is delayed by one hour.

*Chart IV.* The blood-sugar curve is abnormally high and prolonged. The first specimen of spinal fluid contained 0.061 per cent. of sugar; the second, taken  $3\frac{1}{2}$  hours later, contained 0.094 per cent. of sugar. The woman had an enlarged thyroid gland, but there was no exophthalmos.

In the first three cases a definite spinal fluid sugar curve is demonstrated, and Chart IV gives further evidence of its existence. This curve shows delay in starting compared with the blood-sugar curve. The highest sugar readings for the spinal fluid occurred when the blood-sugar curve was in the descendant. Unfortunately the decline of the fluid-sugar curve could not be demonstrated as the patients became restive. The actual rise is a small one, the highest being an increase of 0.033 per cent. in  $3\frac{1}{2}$  hours (Chart IV), but the level attained may exceed the fasting level of the blood (Chart III). The nature of the curve evidently bears a relation both to the height and the prolongation of the blood curve.

#### *Discussion.*

No reference to the existence of a spinal fluid sugar curve can be found in the literature, but high values for the fluid sugar are known to occur in diabetes. For instance, Nixon and Seham found a spinal fluid sugar of 0.729 per cent. associated with a blood-sugar reading of 0.747 per cent. It is obvious that a fuller study of the spinal fluid sugar curve could best be made in severe cases of diabetes. Probably the rise in the fluid of normal persons would be too low to be appreciated.

It might be objected that the spinal fluid curve demonstrated is due to the fact that the fluid was taken from cases of encephalitis where a definite lesion of the vessels of the central nervous system is known to exist. But the blood-sugar charts derived from the cases of intestinal toxæmia mentioned in Table III showed quite unusually high curves, and gave fluid-sugar figures of 0.074 per cent. and 0.099 per cent. after the consumption of glucose. These figures are both above the average fasting level of 0.056 per cent. found in Table I, where the highest fasting level found was 0.070 per cent. Their fluid blood ratios were also high, namely 67 and 106. Similarly, the blood-sugar chart from a case of rheumatic fever (Table III) was unduly high and prolonged. In this case the fluid blood ratio was 87. It is likely that whenever there is an

abnormally high or prolonged blood-sugar curve a spinal fluid sugar curve could be detected without difficulty.

Disregard of the time relationship between lumbar puncture and the intake of food has evidently been responsible for the high spinal fluid-sugar figures obtained from many cases of encephalitis. The high figures also obtained by observers such as Levinson in conditions so diverse as pneumonia, erysipelas, jaundice, and brain tumour could similarly be accounted for, as well as the anomalous relationship between the sugar of the fluid and the blood, in which the fluid sugar equalled or excelled that of the blood.

Alcohol as well as sugar passes readily into the cerebro-spinal fluid. Schottmuller (quoted by Levinson) showed that, after the administration of alcohol, the alcohol was found in higher concentration in the cerebro-spinal fluid than in the blood. It is probable that the estimations were made at a time when the blood-alcohol wave was on the decline and the spinal fluid-alcohol wave at or near its crest.

It is evident that only when specimens of fluid and blood are taken together after a period of fasting can a true ratio between them be obtained. No matter what method of sugar estimation is employed, it would appear that if the ratio is less than 50, the sugar content of the fluid may be said to be decreased; if the ratio were to exceed 70, there would be grounds for claiming the existence of a 'hyperglycorrachia'.

#### *Conclusions.*

1. In epidemic encephalitis the fasting level of the sugar of the blood and the spinal fluid is within normal limits.

2. The blood-sugar curves are in some cases normal; in others they indicate a delay in liver storage. These curves are in no way diagnostic as similar curves are found in other conditions.

3. The fasting level of the spinal fluid sugar is lower than the fasting level of the blood-sugar. In this series the average percentage ratio was 59, with a minimum of 49 and a maximum of 70.

4. Associated with the blood-sugar curve is a spinal fluid sugar curve. This is a delayed curve. The non-recognition of this curve may have been responsible for the high sugar content of the spinal fluid found by many workers in encephalitis and other conditions.

5. A specimen of spinal fluid to be estimated for its sugar content should be taken after 12 hours' fasting along with a sample of blood for similar estimation. If the sugar content of the fluid is normal, its ratio to the blood-sugar should lie between 50 and 70.

6. Specimens of fluid taken at varying intervals after a meal give sugar readings which are valid only when these readings are correlated with the complete sugar curves both of the blood and the spinal fluid.

*Bibliography.*

The sugar content of the cerebro-spinal fluid in cases of epidemic encephalitis became of interest in 1920, when several French physicians found that it was increased above normal. Typical among others, Bourges, Foerster and Marcandier, in a series of six cases, found a hyperglycaemia associated with a hyperglycorrhachia. This increase they considered to be a valuable aid in diagnosis. The methods of estimation employed were not stated, and they accepted as the normal sugar content of the fluid Mestrezat's figure of 0.053 per cent.

The following year Foster (Folin-Wu method) accepted for the average normal content the figure of 0.053 per cent., and obtained figures ranging from 0.053 per cent. to 0.113 per cent., with an average of 0.076 per cent. He concluded that the sugar was increased in the fluid, but he could find no corresponding increase in the blood-sugar.

Coope, using the Folin-Wu method, examined eleven cases of encephalitis and found that in nine of these the fluid-sugar gave a reading over 0.06 per cent.; but of sixty-nine specimens from other diseases, mainly insanities, sixty gave readings over 0.06 per cent. He concluded that 'the French tendency to regard a high sugar content of the spinal fluid as in favour of lethargic encephalitis does not appear to be justified, as figures quite as high occur in other nervous diseases'.

Thalhimer and Updegraff, 1923 (Benedict method), found both a hyperglycaemia and a hyperglycorrhachia. Their figures even for the normal blood and fluid are extraordinarily high. Most of the specimens were taken together after twelve hours' starvation. It is noteworthy that although they considered the spinal fluid sugar to be increased, the fluid blood-sugar ratio in their series was only 45.

Alpers, Campbell, and Prentiss (Benedict-Osterberg method) in thirty-five fluids from encephalitis obtained figures for the sugar content of the spinal fluid running from 0.052 per cent. to 0.115 per cent., with an average of 0.082 per cent. A series of normal fluids gave values of 0.053 per cent. to 0.084 per cent. They concluded that the sugar content of the spinal fluid in encephalitis was generally increased and that the test, though not pathognomonic, was of distinct diagnostic value. However, they obtained figures quite as high in untreated general paralysis and in dementia praecox.

Foster and Cockrell (Folin-Wu method) considering the normal sugar content to lie between 0.04 and 0.06 per cent., found readings over 0.06 per cent. in thirty-four out of thirty-five cases of encephalitis. Similar high readings were obtained in other pathological states, such as brain tumour, gas poisoning, septicaemia, and tabes. They considered that the increase of sugar in the spinal fluid of encephalitis, though not confined to that condition, was useful in making a diagnosis.

## REFERENCES.

- Alpers, Campbell, and Prentiss, *Archiv. Neurol. and Psychiat.*, Chicago, 1924, xi. 653.  
Bourges, Foerster et Marcandier, *Comp. rend. de la Soc. de Biol.*, Paris, 1920, lxxxiii. 914.  
Coope, R., *Quart. Journ. Med.*, Oxford, 1921-22, xv. 1.  
Foster, H. E., *Journ. Amer. Med. Assoc.*, Chicago, 1921, lxxvi. 1300.  
Foster, H. E., and Cockrell, J. R., *Amer. Journ. Med. Sci.*, Philad. and N. York, 1924, N. S., clxvii. 696.  
Levinson, *The Cerebro-spinal Fluid*, Lond., 1924, 50, 97, 146.  
MacLean, H., *Quart. Journ. Med.*, Oxford, 1920-21, xiv. 103.  
Olmsted and Gay, *Archiv. Int. Med.*, Chicago, 1922, xxix. 384.  
Nixon, C. E., and Seham, G. E., *ibid.*, Chicago, 1921, xxviii. 561.  
Schwab, S. I., *Archiv. Neurol. and Psychiat.*, Chicago, 1922, viii. 401.  
Thalhimer, W., and Updegraff, H., *ibid.*, Chicago, 1922, viii. 15.



## PITUITARY OBESITY IN ADOLESCENCE<sup>1</sup>

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With Plates 12 and 13

### *Introduction.*

THAT certain types of obesity were in some way connected with pituitary disease has been recognized since Fröhlich (1) in 1901 first described the syndrome to which Bartels (2) afterwards gave the name of dystrophia adiposo-genitalis. Here in association with a pituitary tumour he found obesity, genital hypoplasia, and lack of growth. Other cases presenting the clinical features of this syndrome were afterwards described by Cushing (3); but in many of the patients there was no evidence of pituitary tumour. He considered that in these cases the disturbance was one of pituitary function only.

In spite of a large accumulation of clinical and experimental evidence, our knowledge of pituitary function is still very imperfect. There are three portions of the gland: the pars anterior, the pars intermedia, and the pars nervosa—the latter two together forming the posterior lobe. The question as to whether these lobes have separate functions, or whether the gland functions as a whole, is still undecided. It is quite certain, however, that the gland is intimately connected with growth, genital function, and carbohydrate metabolism, and a variety of clinical syndromes are met with in which these functions are disturbed to different degrees.

### *Review of Experimental Evidence.*

The pituitary origin of Fröhlich's syndrome was not generally accepted until Paulesco (4), Cushing, Aschner (5), and others first reproduced its main features by experiment on animals. Paulesco was the first to show that partial removal of the anterior lobe leads to obesity. Cushing found obesity and genital hypoplasia and recognized that this condition was identical with the clinical syndrome described by Fröhlich. Since then, other observers have repeated these experiments with varying results. On the whole there was general agreement regarding the genital atrophy, but some difference of opinion as to whether the operation

<sup>1</sup> Received March 26, 1925.

was followed by obesity. Bell (6) did not observe obesity, although in his experience it did follow the operations of compression and separation of the stalk; and Cushing, on clinical grounds, afterwards came to the conclusion that obesity was connected with the functions of the posterior lobe. Experimental removal of the posterior lobe, however, has always been without any obvious effects. Recently Dott (7) has carried out a series of experiments on animals, and has come to the conclusion that, taking all evidence into consideration, this pituitary syndrome, viz. depression of temperature, lethargy, obesity, retardation of growth, and degenerative changes in the thyroid and genital glands, results from partial removal of the anterior lobe, or injury to its blood-supply, or equivalent experiments. This condition, when met with clinically, has been referred to as hypopituitarism. It has frequently been noticed, however, that by no means all the cases of this type of pituitary obesity are characterized by lack of growth, and Cushing has called attention to the fact that in many cases where hypopituitarism is well marked, traces at least of an early tendency to hyperpituitarism in the form of overgrowth can be detected. He attributes this to a preliminary period of activity of the anterior lobe.

#### *Characteristics of the Present Series of Cases.*

In the present paper a series of cases is described, in which the onset of obesity was associated with a period of accelerated growth. These features appear to develop concurrently. Many of the cases also showed disturbances of genital function and of carbohydrate metabolism. The syndrome is apparently of pituitary origin. Sixty patients have been investigated, their ages varying from 8 to 20. Twenty-two of these were males, 38 females. Particular attention has been paid to the following points:

1. Obesity. (a) Type and distribution; (b) comparison of weight with average normal standards for age; (c) aetiology and age of onset of obesity.
2. Presence or absence of a pituitary tumour. (a) Radiographic examination of the sella turcica; (b) ophthalmic findings.
3. Growth. (a) Comparison of height with average normal standards for age; (b) degree of bone development and epiphyseal fusion.
4. General development and genital function. (a) Development of secondary sexual characteristics; (b) age of onset and type of menstruation.
5. Metabolism. (a) Basal metabolism; (b) carbohydrate metabolism; (c) respiratory quotient.
6. Effects of treatment.

1. *Obesity.* (a) *Type and distribution.* Attention has been drawn by Engelbach (8) and other observers to the tendency of pituitary obesity to be located about the girdles, i. e. the hips and the shoulders, whereas the obesity of thyroid origin is more or less generalized. The latter has certain characteristics, such as local padding, of special significance; this feature was described by Gull (9) in 1874. In males, pituitary obesity is characterized by a feminine

type of distribution, the mons and breast development being especially well marked. When the type and distribution of the obesity in our series of cases are analysed, it is found that they can roughly be divided into two groups. In the early cases of recent origin the obesity conforms to the pure pituitary type, whilst in the later cases, in which the individuals have been obese for some considerable time, the obesity tends to be more generalized, though the underlying pituitary characteristics can still be seen.

(b) *Comparison of weight with normal standards for age.* The following table gives details of the increase in weight of our cases above the average normal standards for age. The normal standards used were those of Holt (10) for British children (*Standards of Nutrition*). Our measurements have been taken without clothes; sixty cases have been investigated, and it can be seen that all are grossly above the average weight standards for age.

TABLE I  
*Percentage Number of Cases and Degree of Variation from the Normal Standards.*

Above Average Weight to Extent of	Males.	Females.
25-50 lb.	60 %	55 %
50-100 lb.	33 %	43 %
above 100 lb.	7 %	2 %

(c) *Aetiology and age of onset of obesity.* The following table shows the age of onset of obesity in these cases:

TABLE II		
Males.		Females.
(a) Birth	34 %	(a) Birth 36 %
(b) Between 4 and 7	33 %	(b) Between 5 and 10 29 %
(c) Between 10 and 12	33 %	(c) Between 10 and 16 35 %

It will be seen that approximately one-third of the cases in each group date from birth. Judging from the age incidence of the remainder, the condition seems especially liable to develop about the time of the second dentition or at puberty, especially if any infectious illness occurs at these times. In the males of the series, the onset of obesity in 60 per cent. was considered by the parents to have followed some infectious illness, the child having previously been of normal proportions. The illnesses in these cases were: influenza, measles, scarlet fever, pneumonia, and 'Lincolnshire ague'. It is interesting to note that at the outset, the tendency to obesity was frequently regarded as a sign of satisfactory convalescence. In the female cases a similar history could be obtained in 42 per cent., the illnesses being: diphtheria, influenza, chicken-pox, scarlet fever, rheumatic fever, and tonsillitis with tonsillectomy. It would appear from a study of these facts that a toxic factor is frequently the exciting cause of this condition, though it must be mentioned that in many cases these children were either the sole offspring or the later members of a large family, the parents often showing a distinct tendency to vary from the normal limits of height and weight.

These latter features have sometimes been regarded as the stigmata of pituitary instability.

2. *Presence or absence of a pituitary tumour.* Attention has already been drawn to the fact that hypopituitarism may or may not be associated with a pituitary tumour, the latter condition being referred to by Cushing as primary hypopituitarism. The differential diagnosis depends upon the presence or absence of neighbourhood symptoms (due to pressure of the tumour on surrounding structures). The tumour may arise either within the sella turcica, or beyond its confines in the interpeduncular space. In the former case, Cushing has shown that it produces an alteration in the size of the sella, whilst in the latter, where the tumour is extra-sellar, there is often a widening of the entrance to the fossa. In either case disturbance of vision may occur owing to involvement of the cranial nerves.

(a) *Radiographic examination of the sella turcica.* In the majority of the present series of cases the pituitary disturbance seemed to be one of function, as few instances of neighbourhood symptoms occurred. Radiographic examinations of the sella turcica were made in all cases, and particular attention was directed to the following points: (i) size, (ii) shape, (iii) entrance, (iv) any tendency to erosion.

(i) *Size.* In 36 per cent. the size of the sella appeared to be quite within the normal limits. In only two cases was it definitely enlarged, and in neither case was there any other evidence of pituitary tumour. In 60 per cent. the sella was very definitely smaller than normal, and in a few cases it appeared from X-ray examination to be almost microscopic. This condition of an abnormally small sella has been described by Cushing in his cases of primary glandular hypoplasia in the young. Plate 12, I, represents a typical instance in a boy of 14, whose photograph is shown in Plate 13, V. A normal sella is shown for comparison in Plate 12, II.

(ii) *Shape.* In 68 per cent. the sella was more or less circular; nearly all the cases mentioned above where the size was also normal fall into this group. In 32 per cent. the sella was definitely flattened, and in nearly all these cases it was considerably below the normal size.

(iii) *Entrance.* In the majority of cases, 68 per cent., the entrance to the fossa appeared to be of normal dimensions; but a marked tendency to approximation of the clinoid processes was observed in 24 per cent., creating, when viewed laterally, a roof to the sella. In a certain number of these cases the anterior and posterior clinoid processes appeared to be completely fused. Plate 12, I, illustrates this condition. In only one case of the series did the entrance to the fossa appear to be unduly widened, and here also the visual fields showed a tendency to contraction.

(iv) *Erosion.* In 96 per cent. the outline of the sella was well defined and there seemed to be no question of erosion. In the remaining cases it was doubtful, and in one, in which there appeared to be some erosion of the anterior and posterior clinoid processes, there was also found a marked general contraction of the visual fields.

From these radiographic observations of the sella turcica it would appear that the majority of cases of pituitary obesity of this type are associated, when any variation from the normal is found, with a sella turcica which is characteristically below the normal size. A tendency to approximation of the anterior and posterior clinoid processes is also seen. In very few cases of the present series does radiographic examination of the sella turcica show any evidence of a pituitary tumour.

(b) *Ophthalmic findings.* Characteristic changes in the visual fields have been described by Cushing in cases of hypopituitarism with pituitary tumour. He regards these disturbances as the most serious of all neighbourhood symptoms. The typical changes can be divided into two groups, peripheral and central. In the peripheral visual field the loss starts in the upper and outer quadrant and progresses clockwise in the right field and counter-clockwise in the left field, so that the upper nasal quadrant is the last part of the field to be lost. Coincident with the peripheral field changes, a central defect or scotoma develops, behaving in exactly the same way as the peripheral defect, in that the scotoma starts to the upper and outer side of the fixation point and spreads round the fixation point clockwise in the right field and counter-clockwise in the left field.

Routine examinations of the optic disks and visual fields were carried out in the majority of the present series of cases. A single test object only was employed. The results show that in the majority of cases examined the optic disks were normal and the fields full. Pallor of the disk was noted in only two cases, whilst in only five of the series was there any defect in the visual fields. In these there was a marked tendency to a general concentric contraction. It seems doubtful how much importance should be attached to this feature without a more complete examination, but it must be mentioned that none of these cases presented any further definite evidence of pituitary tumour. Details of cases showing eye changes are given in Table III.

TABLE III

	Optic Nerves.	Visual Fields.	Sella Turcica.
Case 1	Pallor of disks	Marked contraction, especially bitemporal	Abnormally small
Case 2	Pallor of disks	Full	Normal
Case 3	Normal	Marked contraction, especially bitemporal	Small
Case 4	Normal	Marked contraction, especially bitemporal	Normal
Case 5	Normal	Marked general contraction	Normal
Case 6	Normal	Marked general contraction	Small

3. *Growth.* Modern observers all agree that, in dealing with the pituitary and its effect on growth, the anterior lobe alone need be considered. All recent experimental evidence points to this. It has already been mentioned that partial removal of the anterior lobe in animals leads, among other symptoms, to lack of development of the skeleton with undergrowth. On the other hand,



feeding experiments with anterior lobe extracts have now been shown to produce an acceleration of growth. For a time a difference of opinion existed as to the results of these experiments, but it is now generally considered that this could be explained by the absence of any test of the physiological activity of the preparations used. Since then, however, a considerable number of experiments have been carried out, which show that a definite acceleration of growth can be obtained by the administration of anterior lobe extracts. Positive results were obtained by Schäfer (11), Goetsch (12), Uhlenhuth (13), and Marinus (14), whilst recently Dott carried out a series of successful feeding experiments with kittens and dogs. In reviewing the literature he concluded that it is now generally accepted that growth, in so far as it concerns the pituitary gland, is definitely related to the functions of the anterior lobe. Clinical evidence also points to the fact that the rate of growth of individuals is related to the state of activity of the anterior lobe. Cushing has long been of the opinion that overactivity of this lobe, before fusion of the epiphyses has taken place, leads to gigantism, whilst underactivity leads to skeletal infantilism. It must be remarked here, however, that Dott, as a result of his recent feeding experiments in animals, has come to the conclusion that although anterior lobe feeding produces an acceleration of growth, it does not lead to gigantism, for although the animals grow faster and mature earlier, their epiphyseal cartilages ossify sooner and the animals remain within the normal limits of stature.

The present series of cases presents some very interesting features from this point of view and seems to confirm clinically the experimental findings of Dott.

(a) *Comparison with average standards of height for age.* We have compared the heights of our patients with the average normal standards for age of British children (Holt, *Standards of Nutrition*). In the younger patients overgrowth is a characteristic feature of these individuals, whereas the older individuals show little tendency to vary from the normal standards. These points are well illustrated by the following table (IV), which shows the ages of the individuals in column I, and the number of cases in each age group in column II. In column III is represented the average increase in height above the normal standards for each age group. Column IV shows the proportion of patients more than +10 cm. above average height, while column V shows the proportion in each group more than -5 cm. below the normal standards.

This clearly shows that the younger individuals tend to be more consistently above average height for age than the older, and suggests that an early period of accelerated growth takes place in these cases. Plate 13, III, shows a typical instance in a boy of 9. His brothers, aged 8 and 4, are shown on his right and left in the photograph. The same point could be demonstrated by individual growth curves, for a history of accelerated growth with early cessation at or about puberty could be obtained in the majority of our cases. It has not been possible, however, to observe any untreated individual case for a sufficiently long period of time to demonstrate this point. The older patients, on the other hand, do not appear to vary much from the normal height standards.



In some cases they are definitely below them, though this was not a feature in any of the younger patients. The results would appear to be explicable on the hypothesis of a preliminary period of anterior lobe hyperactivity. This would result in accelerated growth and premature maturation of the skeleton. It will be shown in the following section that these suggestions are amply confirmed by X-ray examination of the bone development and epiphyses of our cases.

TABLE IV

I. Age.	II. No. of Cases examined in each Age Group.	III. Average Increase in Height in cm. above normal for each Group.	IV. % No. of Cases in each Group more than + 10 cm. above average Height.	V. % No. of Cases in each Group more than - 5 cm. below average Height.
			%	%
8	1	+ 18	100	0
9	5	+ 11.2	60	0
10	4	+ 11.5	75	0
11	4	+ 9.5	50	0
12	5	+ 8.6	48	0
13	6	+ 6.8	48	0
14	6	+ 4.3	36	17
15	6	+ 4.3	0	0
16	4	+ 4.7	50	17
17	5	- 1.2	0	34

(b) *Bone development and epiphyseal fusion.* It is only to be expected that underlying these disturbances of growth in pituitary disease comparable changes would be found in the development of the bones and epiphyses. In point of fact the bone changes found in acromegaly, gigantism, and Fröhlich's syndrome have been frequently described; but until lately no accurate observations have been made in animals as to the result of pituitary ablation or feeding experiments. Dott and Fraser (15), however, have now investigated this question for the Medical Research Committee (1918), and their results are embodied in a paper by the former already discussed. They conclude that very striking alterations of bone and epiphyseal development do take place as the result of pituitary disorder. Partial removal of the anterior lobe causes a decrease in epiphyseal activity. In seven experiments the average decrease in epiphyseal activity was 57 per cent. Feeding experiments with anterior lobe extracts cause an increase of epiphyseal activity. In four experiments the increase was 22 per cent. Corresponding histological changes were observed. In deficiency the cartilage undergoes a true degeneration, and a diminution of activity takes place at the ossifying junction. Feeding experiments, on the other hand, lead to an excessive growth of cartilage with proliferation of its cells and an intense ossification at the epiphyseal junction. Radiological studies confirm these findings, and show that in deficiency epiphyseal union is delayed, whilst in the feeding experiments the cartilage tends to mature more rapidly and ossify earlier.

We have made radiographic investigations of the bone and epiphyseal development of the hands and wrists in fifty of our cases. The results are entirely in keeping with the above experiments. It has already been mentioned

that our cases show evidence and give a characteristic history of a period of premature and accelerated growth, presumably the result of increased anterior lobe activity. When fully developed these individuals do not vary much from the normal limits of stature, for this acceleration of growth is not maintained for long after the period of puberty. Clinically, attention must also be called to the abnormally large and solid bones found in these cases; this is especially well seen in the hands and feet. In the cases in which the evidence of accelerated growth is most marked, the hands and feet tend to be abnormally large. Radiographic examination shows an advanced degree of development of the bones. Not only are they larger and more dense than the normal, but complete epiphyseal fusion of the individual bones is frequently found to have taken place four or five years before the normal time. This condition of complete fusion is found more noticeably in the females than in the males, though the latter also show very definite premature development. The degree of bone development would appear to depend upon the degree of anterior lobe activity, for it is most advanced in those individuals who show the greatest acceleration of growth. Plate 12, IV, shows the condition in a typical case: a boy of 14 who also exhibited marked overgrowth with obesity, Plate 13, V. It can be seen that the epiphyses of the phalanges are completely fused to the diaphyses at this early age, whereas in the normal individual this should not have taken place until the eighteenth to the twentieth year.

4. *General development and genital function.* As already discussed, the anterior pituitary lobe has been shown to exert a marked effect on general development and genital function. Anterior lobe deficiency in young animals, the result of partial removal, causes a syndrome of infantilism (Paulesco, Cushing, Aschner, and Dott). The animals remain infantile in size, in configuration, in behaviour, and in sexuality. Further, hyperpituitarism (anterior lobe) produced by anterior lobe feeding causes an acceleration of development, as shown by the more rapid assumption of mature configuration and the earlier functional activity of the sexual glands.

Clinical reports of cases of pituitary obesity have generally emphasized the tendency of these subjects to lack of growth and genital hypoplasia, signs of anterior lobe deficiency; but we have already called attention to the fact that *many of these cases show traces of an early tendency to anterior lobe overactivity in the form of overgrowth.* The same tendency is noticeable in the case of their genital development. Biedl (16) has recently described a series of 32 cases of this syndrome in which genital atrophy was only present in 12. In our own series we have made a thorough investigation of the general and genital development in 48 cases, 32 females, 16 males. Twenty-one of these, 10 females and 11 males, had not reached the age of puberty when they came under observation. Their average age was  $10\frac{1}{2}$  years. The general development in all was well up to the average, when compared with normal children; in fact, in the case of the male, the secondary sexual characteristics were well developed at the age of 10.

More definite evidence of premature development, however, could be obtained from the older children, and this was especially noticeable in the females. This series comprises 27 cases—22 females, 5 males—all of whom had reached the age of puberty. It is generally assumed that in British children puberty occurs, on an average, between the ages of 13 and 16 in females, and 14 and 16 in males, as evidenced by the development of the secondary sexual characteristics, and in females also by the onset of menstruation. We have investigated in our female cases the age of onset and the type of menstruation. The following Table (V) shows the age of onset in this group of 22 cases :

TABLE V

Age of Onset.	No. of Cases.	% No. of Cases in each Age Group.
11	1	5
12	9	41
13	10	45
14	2	9

It can be seen that in a large majority of these subjects menstruation commences between the ages of 12 and 13, which is distinctly earlier than in the average child, and no instance occurs of the onset of menstruation being later than 14. Further interesting information is obtained from a study of the type and menstrual rhythm in these cases. In the majority, 73 per cent., the type and rhythm were quite normal for a few years. In a few cases, 27 per cent., menstruation at the start tended to occur too frequently, at intervals of less than the usual twenty-eight days ; and in these cases also, the losses tended to be greater than the average. On the other hand, when the whole group of twenty-two cases is taken into consideration it is seen that, after a varying period of normal or excessive menstruation, 59 per cent. developed ultimately a tendency to delayed and scanty menstruation and periods of amenorrhoea. This is in keeping with Cushing's observation that states of hyperpituitarism tend ultimately to pass into states of hypopituitarism.

The secondary sexual characteristics were well developed in all these cases, both male and female, whilst in a few, 7 females and 2 males, development was definitely greater than the average for their age.

5. *Metabolism.* (a) *The basal metabolism.* It has been shown by Plaut (17) that in obesity of pituitary origin the oxygen consumption is reduced and the basal metabolic rate lowered. Benedict and Homans (18) have also demonstrated that the carbon dioxide exchange is diminished. Further indications of lowered metabolism are seen in the lethargy, slow pulse, and subnormal temperature of many of these cases. The low temperature has been attributed to deficiency of the anterior lobe, and can be experimentally reproduced in animals by partial removal of this lobe ; subsequent injections of anterior lobe extract restoring it temporarily to normal (Cushing). More recently Dott has pointed out that in continued anterior lobe feeding the temperature of the experimental animals is

consistently slightly above that of the controls. The evidence would appear therefore to be in favour of the anterior lobe exerting an influence on metabolism.

We have investigated the basal metabolism in a considerable number of the present series of cases. The method used has been that described by Cathcart (19): a sample of expired air is collected over a period of ten minutes in a Douglas bag, with the patient at rest and in the post-absorptive condition. This sample is analysed for its oxygen content, from which the patient's calorie production can be calculated and compared with the normal standards of Dubois.

The following table (VI) shows the basal metabolic results obtained in 28 of our cases who had received no previous treatment of any kind for their obesity. The remainder had for various periods been treated with thyroid or other extracts and are not included in the table.

TABLE VI  
*Basal Metabolism in 28 Previously Untreated Cases.*

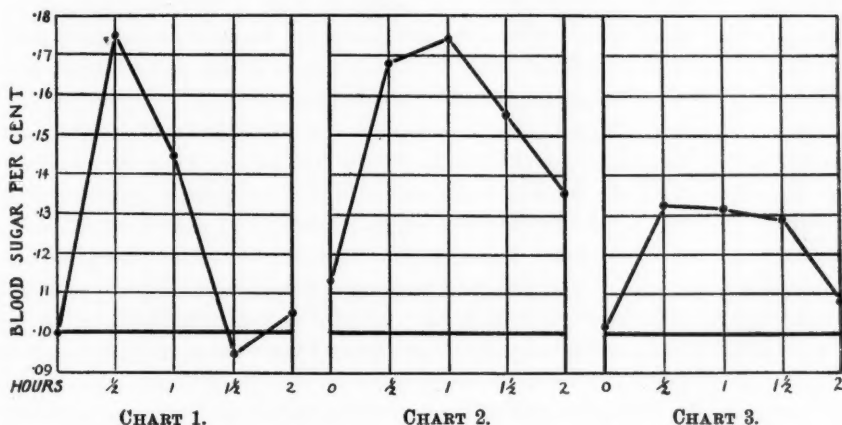
	% No. of Cases.
	%
(1) Within normal limits (+10 % and -10 %)	32
(2) Greater than +10 %	0
(3) Between -10 % and -20 %	28
(4) Between -20 % and -30 %	25
(5) Greater than -30 %	15

From this table it can be seen that 68 per cent. of this series have basal metabolic rates below the normal limits of +10 per cent. to -10 per cent. The remaining 32 per cent. fall within the normal limits, no instance occurring of a rate greater than +10 per cent. We have attempted to trace some connexion between the degree of metabolism and the following features, which we thought might depend on it: (1) the degree of obesity; (2) the duration of obesity. There would, however, appear to be little relation between the basal metabolic rate and the degree of obesity. On the whole, the more obese patients show a tendency to slightly lower readings, but the difference is so slight when averaged that much importance could not be attached to it. Likewise the duration of obesity does not appear to bear much relation to the basal metabolic rate, though on the whole this appears to be slightly lower in the cases of longest duration.

It has been pointed out, however, by Dott and others, that in experiments in animals after partial removal of the anterior lobe, changes of a degenerative nature occur later in the thyroid gland. As it is generally accepted now that the latter gland plays a more vital part in the regulation of the basal metabolic rate than any other, it is possible that the lower readings obtained in the cases of longer duration might be explained on the basis of a secondary thyroid deficiency.

(b) *The carbohydrate metabolism.* It has long been known that carbohydrate metabolism is disturbed in pituitary obesity. Goetsch, Cushing, and Jacobson (20) have all drawn attention to the fact that the tolerance for sugar in many of these individuals is greatly increased, and this feature has been shown to be of con-

siderable diagnostic importance. The earlier observers carried out carbohydrate tolerance tests by estimating the capacity of the individual to deal with large doses of sugar without excreting it in the urine; but since modern methods of estimating the sugar in the blood have been devised, recent tests have been based on the type of blood-sugar curve obtained after the administration of 50 gm. of glucose. A considerable number of sugar tolerance estimations were made in the present series of cases; the method of estimating the blood-sugar used was that of MacLean (21). The fasting blood-sugar was determined, 50 gm. of glucose were given, and further estimations of the blood-sugar made at half-hourly intervals for two hours. Chart 1 shows the curve obtained in a series of normal individuals and may be accepted as a normal standard (MacLean). Charts 2 and 3 show the averages of two types of curves obtained in 20 of our patients who



had received no previous endocrine treatment of any kind. On analysis it was found that these 20 cases could be divided into two groups on a basis of the duration of their obesity. In Chart 2 the average duration of obesity in 13 cases was two years; in Chart 3 the average duration of obesity in 7 cases was nine and a half years.

It is quite obvious that the curves in these two groups of patients differ very considerably from the normal. They also differ entirely from one another. In the first group, Chart 2, where the onset of obesity is of comparatively recent origin, the curve approaches to the normal height, but the fall in blood-sugar is very delayed. The individual is apparently unable to deal with 50 gm. of glucose as rapidly as the normal person. The renal threshold in these cases is not altered, for when the blood-sugar approaches the level of 0.18 per cent., sugar appears in the urine. Briefly, the sugar tolerance is decreased. In the second group, Chart 3, the blood-sugar curve never reaches anything like the normal level, the reading obtained at the end of one and a half hours differing only slightly from that obtained at the end of half an hour. In none



of these cases did sugar appear in the urine. The sugar tolerance in this group is increased.

The first type of curve apparently represents the early stage, the second type the later stage of this condition.

These results are very interesting in connexion with certain observations that have already been made pointing to the conclusion that the earlier stages of the disease frequently manifest evidence not of hypofunction, but of increased activity of the pituitary gland. If the decrease in sugar metabolism be accepted as an indication of increased endocrine activity, it is obvious that in all the cases of short duration mentioned there is a certain amount of pituitary hyperactivity. Later on, this increased function gives place to a hypoactivity which is reflected in the very much increased sugar metabolism seen in all the cases of long duration. In the light of our present knowledge it is difficult to explain why decreased pituitary activity should be associated with a definite increase in carbohydrate metabolism. We now know, however, that the administration of insulin to diabetic individuals very frequently results in the patient becoming exceedingly fat. We also know that pituitrin neutralizes the effect of insulin. It might therefore be argued that in the normal individual the effect of insulin is to some extent governed and inhibited by the pituitary. When the pituitary is no longer active the natural result would be for the insulin to become more active. This would lead to increased sugar tolerance and deposition of fat—exactly the condition found to be present in the patients described. It is, therefore, very probable that the increased sugar tolerance and deposition of fat seen in these patients depends on a hyperactivity of insulin which is no longer controlled in the normal manner by the pituitary hormone.

(c) *Respiratory quotient.* In carrying out the basal metabolism experiments in these patients it was noticed that the respiratory quotient was almost invariably low and in the neighbourhood of 0.7, a quotient which is usually taken to indicate oxidation of fat, the oxidation of protein being indicated by the quotient 0.8 and of carbohydrate 1.0. The tendency to a low respiratory quotient in these patients appeared to be anomalous, when their tendency to increased carbohydrate consumption and storage of fat was taken into consideration. It was decided therefore to investigate the behaviour of the respiratory quotient after the administration of sugar, to ascertain whether it differed in any way from that of normal individuals. A series of experiments was carried out in five of our patients and in six normal individuals, medical students who appeared to be representative of the average healthy person. The respiratory quotient was obtained by the method described by Cathcart; the apparatus and mode of experiment were the same as we have described for the determination of the basal metabolism. The fasting respiratory quotient was first determined, 50 gm. of sugar were then given, and further estimations of the respiratory quotient were made at half-hourly intervals for two hours. The subjects were allowed to walk about between the experiments. The actual results we obtained are given in the following tables. Table VII gives the actual respiratory quotient figures



obtained in the series of normal individuals; the respiratory quotient in every case rises to 1 before the completion of the experiment. Table VIII gives the figures obtained in our five patients. Here it can be seen that in every case the fasting respiratory quotient is low and in the neighbourhood of 0.7, and after the administration of sugar it fails to rise, as in the cases of the normal controls. Fig. 4 represents the average respiratory quotient curves obtained from these two groups.

*Respiratory Quotient after 50 grm. Sugar.*

TABLE VII

Normals.	Fasting Quotient.	$\frac{1}{2}$ hour.	1 hour.	$1\frac{1}{2}$ hours.	2 hours.
1	0.83	0.94	1.0	0.99	0.87
2	0.96	0.94	1.05	—	—
3	0.75	1.0	1.0	—	—
4	0.87	0.99	1.0	1.0	0.89
5	0.81	0.91	0.95	1.0	—
6	0.98	0.98	1.04	1.06	0.98

TABLE VIII

Patients.	Fasting Quotient.	$\frac{1}{2}$ hour.	1 hour.	$1\frac{1}{2}$ hours.	2 hours.
1	0.70	0.76	0.78	0.78	0.79
2	0.74	0.77	0.79	0.78	0.82
3	0.75	0.73	0.78	0.77	0.81
4	0.74	0.76	0.78	0.78	0.78
5	0.75	0.77	0.76	0.81	0.85

It would thus appear that the increased power to deal with sugar is not in any way dependent on increased oxidation. There must therefore be an increased power of storage—a condition associated with the increased amount of fat present.

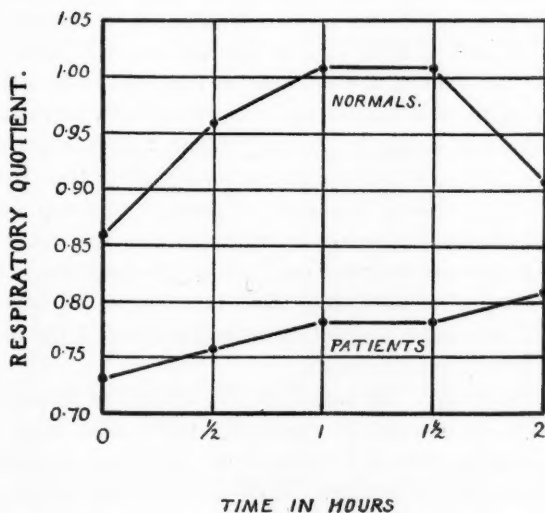


CHART 4.

Z

6. *Treatment.* The majority of the present series of cases have been treated with a combination of thyroid and whole gland pituitary extracts. A few have been treated with thyroid alone and a few with whole gland pituitary, but a combination of the two in gradually increasing doses has produced the most satisfactory results. It has been known for some time that thyroid extract often has a beneficial effect in reducing the obesity of some of these individuals. Others, however, seem unable to tolerate it in sufficiently large doses to produce an effect. This difficulty appears to be overcome by combining it with whole gland pituitary extract, which apparently improves the tolerance to thyroid. On theoretical grounds the combination of anterior lobe extract with thyroid would appear to be indicated, but we have preferred to use extracts of the whole gland owing to recent evidence which has demonstrated that pituitrin (posterior lobe extract) has a stabilizing effect on the blood-sugar. Burn (22) has shown that injections of pituitrin not only inhibit the hyperglycaemia produced by adrenalin, but also inhibit the fall of blood-sugar produced by insulin. Thyroid, when administered by itself, produces hyperglycaemia, and it is possible that the increased tolerance to thyroid obtained by combining it with whole gland pituitary has something to do with the stabilizing effect on the blood-sugar of the posterior lobe extract.

*Mode of administration.* In our cases desiccated extracts of thyroid and of whole gland pituitary (Armour's) have been administered by the mouth in gradually increasing doses. We started with small doses, gr.  $\frac{1}{2}$  of thyroid and gr.  $\frac{1}{2}$  of pituitary every night, and gradually increased the dosage until 5 or more grains of each extract were being taken three times a day. This treatment was continued until a definite effect on the metabolism and obesity was obtained; this generally occurs in the course of the first three or four months, though during the early stages, with the smaller doses, a slight increase in weight is often seen. At the end of three or four months, however, these patients have generally lost a stone or more in weight, and at this stage treatment is suspended for a month or so, to be continued again at the end of that time. During the interval an increase in weight is generally found, but subsequently a further reduction can be made and maintained on smaller doses than those originally prescribed. We have treated a number of cases in this way during the last three years, with alternating periods of treatment and rest, and we have found that the intervals between treatment can gradually be lengthened and the dosage reduced. The metabolism ultimately tends to revert to its original condition more slowly. If treatment, however, is entirely suspended, the improvement is not maintained for any length of time.

*Results of treatment.* The results of this method of treatment have been most satisfactory, the obesity in practically every case being considerably lessened. In the cases of short duration, these individuals can often be reduced to comparatively normal proportions. In the cases of longer duration, the results have been most striking. In one case, that of a boy aged 14, who had been stout from birth and who, when he came under observation two years previously,

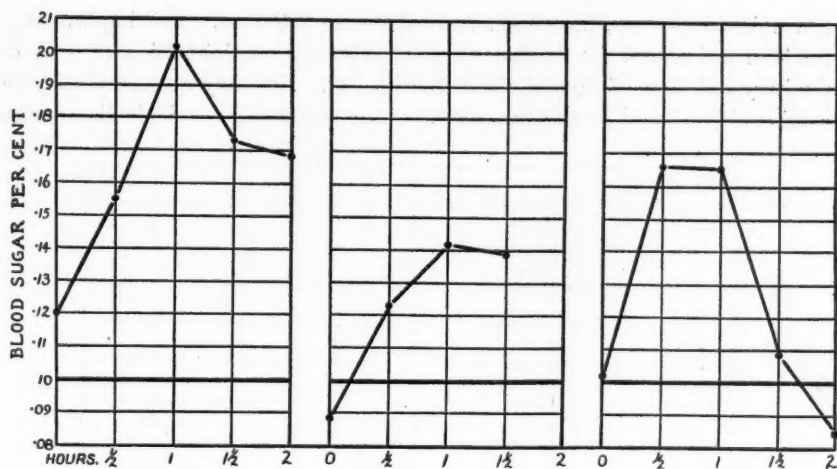


CHART 5.

CHART 6.

CHART 7.

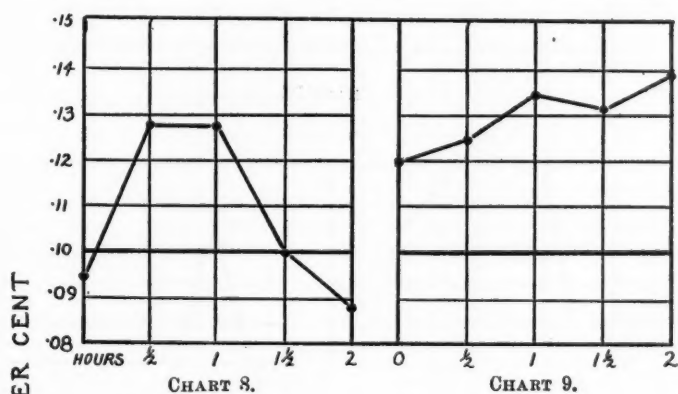


CHART 8.

CHART 9.

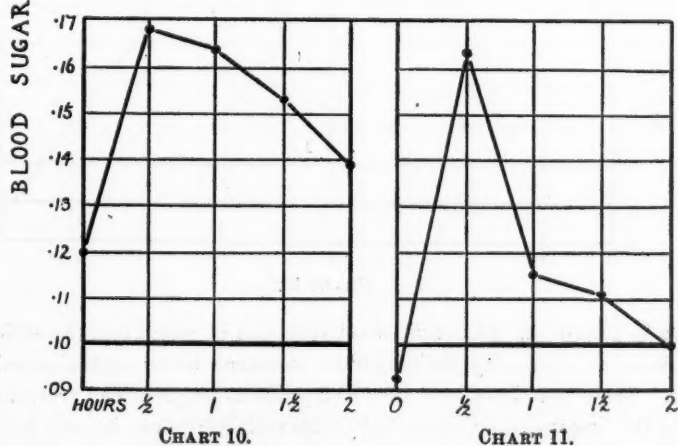


CHART 10.

CHART 11.

had weighed 24 stone, the weight was reduced to  $13\frac{1}{2}$  stone. This improvement has been maintained for the last six months by the administration of 5 gr. of pituitary and 5 gr. of thyroid three times a day. Not only can the obesity be considerably reduced by this treatment, but the underlying metabolic disturbance

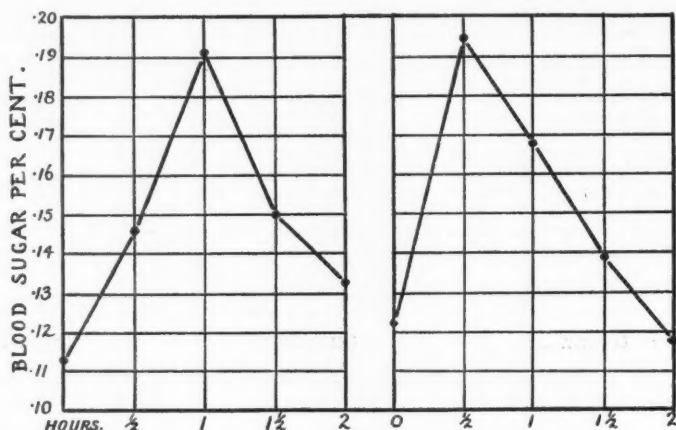


CHART 12.

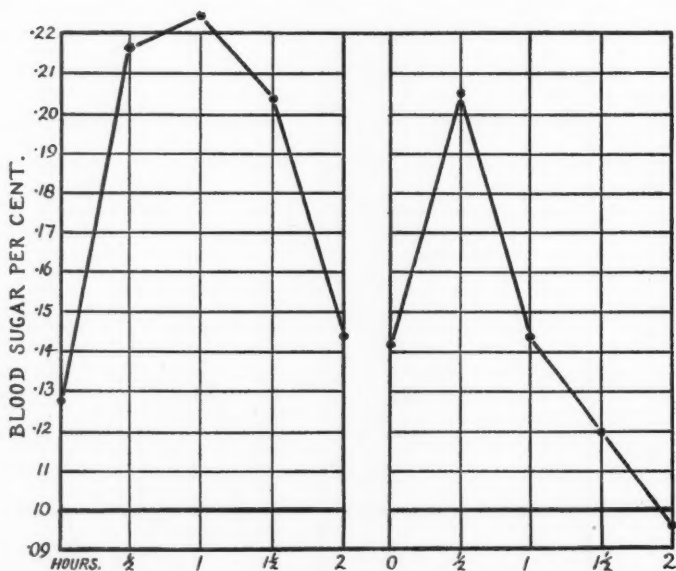


CHART 13.

can also be improved. The basal metabolism can be raised and the carbohydrate metabolism, as shown by carbohydrate tolerance tests, approximated to the normal. These tests have been used as a guide to progress and treatment. The effect of this treatment on the carbohydrate metabolism can be seen from a study

of the charts. We have already described in a previous section of this paper how, in the early stages of this condition, the blood-sugar curves are high and delayed, whilst in the later stages they are low. The effect of treatment is to approximate both types of curve to the normal. Charts 5, 6, and 7 represent the effects of treatment in an early case. Charts 8, 9, 10, and 11 represent the effects of treatment in a case of longer duration.

Charts 12 and 13 show the effect of treatment with whole gland pituitary extracts alone in two cases, one male and one female. This treatment had no effect on the obesity of these individuals, in spite of the fact that the sugar tolerance curves show some improvement. In the second of these cases, however, the effect on menstruation was most striking; previously to treatment, menstruation had occurred at intervals of two, three, or four months. During the four months this patient was under treatment, menstruation occurred regularly at the following intervals: 33 days, 28 days, 28 days.

#### *Summary.*

A series of 60 cases of adolescent pituitary obesity has been described, in which the primary disturbance, judging by the absence of neighbourhood symptoms, seems to be one of pituitary function. Apart from the obesity, the chief characteristic of these individuals is an early tendency to overgrowth and premature development, which appears to be due to hyperpituitarism (anterior lobe hyperactivity). This condition finally passes into hypopituitarism. When fully developed these individuals are not abnormally tall and are often below the average height, for fusion of the epiphyses occurs prematurely and results in an early cessation of growth. Obesity develops concurrently with the overgrowth and is associated with an underlying disturbance of carbohydrate metabolism. In the early stages there is an inability to utilize carbohydrate, in the later stages an increased sugar tolerance. Examination of the respiratory quotient after the administration of sugar shows that the increased power to deal with carbohydrate in the later stages is not in any way dependent on increased oxidation, but due rather to an increased power of storage—a condition associated with the increased amount of fat present. It is suggested that this may in some way be connected with a hyperactivity of insulin, which is no longer controlled in the normal manner by the pituitary hormone. A marked improvement in the metabolism of these individuals can be effected by treatment. The basal and carbohydrate metabolism can be restored to normal and the obesity considerably reduced, but as far as it is possible to tell at present the metabolism appears to revert to its original condition, if treatment is suspended.

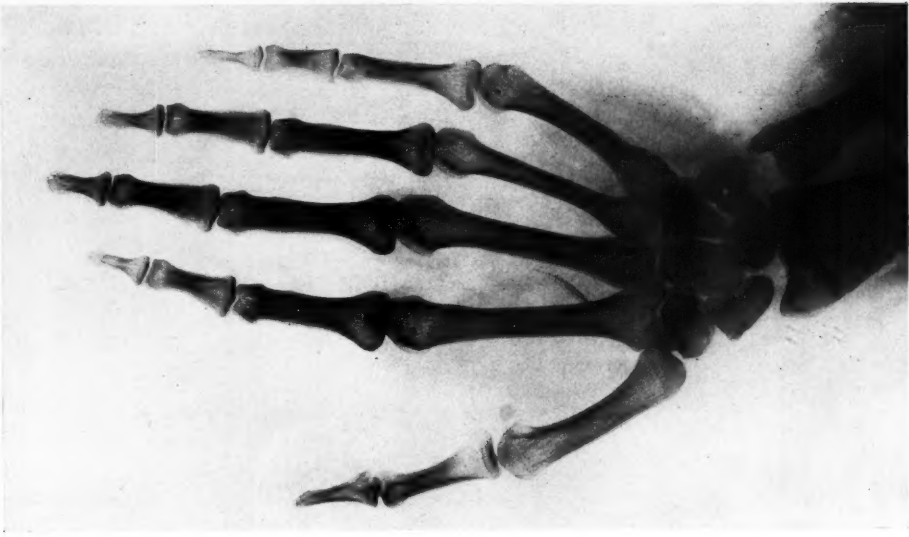
We wish to express our indebtedness to Professor Hugh MacLean, Director of the Medical Unit, St. Thomas's Hospital, under whose guidance this research

has been carried out; also to Mr. P. G. Doyne, for investigating the ophthalmic conditions and for contributing the ophthalmic report to this paper; and to Dr. G. Fildes for carrying out the radiographic examinations of these cases.

## REFERENCES.

1. Fröhlich, A., *Wien. Klin. Rundschau*, 1900, xv. 883.
2. Bartels, *München. Med. Wochenschr.*, 1908, lv. 201.
3. Cushing, Harvey, *The Pituitary Body and its Disorders*, Lond., 1912.
4. Paulesco, N. C., *L'Hypophyse du Cerveau*, Paris, 1908.
5. Aschner, B., *Wien. Klin. Rundschau*, 1909, xxii. 1730.
6. Bell, W. Blair, *The Pituitary Body*, Lond., 1919.
7. Dott, Norman M., *Quart. Journ. Exp. Physiol.*, Lond., 1923, xiii. 241.
8. Engelbach, Wm., *Med. Clin. N. America*, Philad., 1922, vi. 16.
9. Gull, W., *Trans. Clin. Soc.*, Lond., 1874, vii. 181.
10. Holt, L. Emmett, *Amer. Journ. Dis. Child.*, Chicago, 1918, xvi. 359.
11. Schäfer, E. A., *Proc. Roy. Soc.*, Lond., 1909, Ser. B, lxxxi. 442.
12. Goetsch, E., *Johns Hopkins Hosp. Bull.*, Baltimore, 1916, xxvii. 29.
13. Uhlenhuth, E., *Proc. Soc. Exp. Biol.*, 1920, xviii. 11.
14. Marinus, C. J., *Amer. Journ. Physiol.*, 1919, xlix. 238.
15. Dott, N. M., and Fraser, J., *Report to Med. Research Com.*, Lond., 1918.
16. Biedl, A., *Internal Secretory Organs*, N. York and Lond., 1912.
17. Plaut, R., *Deutsches Arch. f. Klin. Med.*, Leipzig, 1923, cxlii. 266.
18. Benedict, C., and Homans, J., *Journ. Med. Research*, Boston, 1911-12, xxv. 409.
19. Cathcart, E. P., *Journ. Roy. Army Med. Corps*, Lond., 1918, xxxi. 339.
20. Goetsch, E., Cushing, E., and Jacobson, G., *Johns Hopkins Hosp. Bull.*, Baltimore, 1911, xxii. 165.
21. MacLean, E., *Modern Methods in Diagnosis and Treatment of Glycosuria and Diabetes*, Lond., 1924.
22. Burn, J. H., *Journ. of Physiol.*, Lond., 1922-3, lviii. 318.



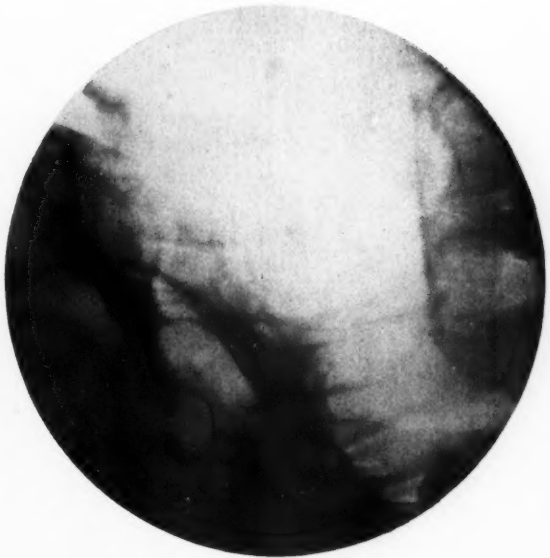


IV



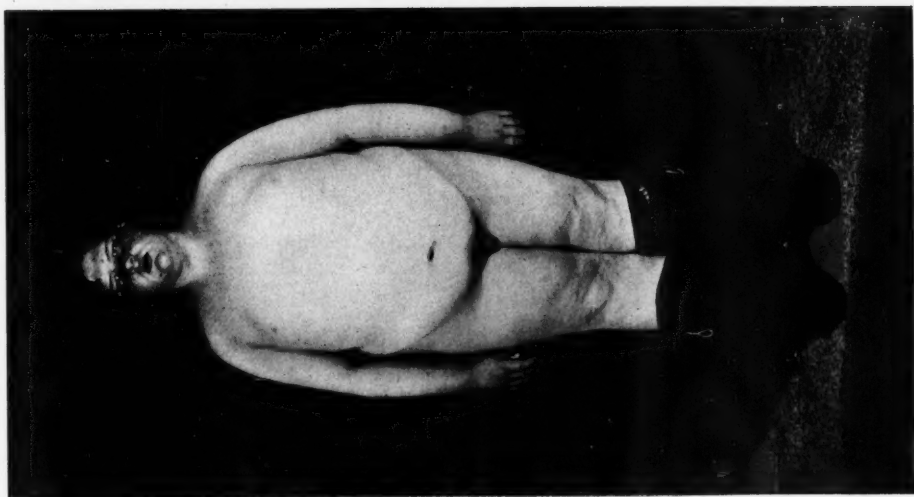
I

Small sella seen 1 cm. below arrow



II







CARBOHYDRATE TOLERANCE IN MYXOEDEMA<sup>1</sup>

BY H. GARDINER-HILL, P. C. BRETT, AND J. FOREST SMITH

(From the Medical Unit, St. Thomas's Hospital)

*Carbohydrate Tolerance in Myxoedema.*

THERE seems to be general agreement that the blood-sugar curves obtained in most cases of hyperthyroidism tend to reach a greater height and to be more prolonged than in normal individuals. Thus Dennis and Aub (1) state that alimentary hyperglycaemia was observed in every one of their cases of hyperthyroidism. Morris (2), Sanger, Hamman and Hirschmann (3), agree with this, although Janney and Isaacson (4) did not find the hyperglycaemia constant. Sanger and Hun (5) showed that the explanation of this hyperglycaemia probably results from some defect in the storage mechanism.

Table I shows the results obtained by us in four cases of severe exophthalmic goitre. The fasting level is shown, and the blood-sugar content at half-hourly intervals after the ingestion of 50 gm. of glucose. The urine was examined for sugar by testing with Fehling's solution. In each the blood-sugar rose above 200 mg. per 100 c.c. of blood, and the curves show definite prolongation after 50 gm. of glucose had been given. Glycosuria was present at the end of the test in each case.

A study of the literature shows that less attention has been paid to the blood-sugar curves in cases of myxoedema. Thyroid ablation experiments on animals, where care was taken to preserve the parathyroids, were usually followed by hypoglycaemia, and certain observers, as Janney and Isaacson (4), found low blood-sugar curves in patients suffering from hypothyroidism. Flesch (6), on the other hand, states that in two cases of myxoedema there was a hyperglycaemia following the ingestion of glucose equal to that observed by him in hyperthyroid cases, and that this hyperglycaemia was still further increased by the implanting of healthy human thyroid. Geyelin (7) reports a low-fasting level in myxoedematous patients (53-68 mg. per cent.). Grey (8), in a full report on eight cases of hypothyroidism, states the average curve is only slightly lower than that obtained in his series of patients with hyperthyroidism.

This paper records the findings in fifteen well-marked cases of myxoedema seen during the last three years among hospital out-patients. In all the basal metabolic rate was estimated to confirm the diagnosis. The method adopted in

<sup>1</sup> Received March 26, 1925.

estimating the blood-sugar was that of MacLean (9). The patients were instructed to have a light breakfast at 8, and the fasting level of the blood-sugar was ascertained some five hours later. Fifty grm. of glucose dissolved in 100 c.c. of water were then given, and the blood-sugar was estimated every half-hour for two hours in the majority of cases; in two cases the last reading was obtained one and a half hours after the injection. At the end of the test the urine was examined to see if it reduced Fehling's solution. A possible objection may be raised that the fasting level determined in this way may not give a true value owing to the impossibility of preventing the patient having food between the breakfast and reporting at the laboratory. Four of our results were obtained from patients who were admitted to hospital to ensure definite fasting, and their results do not differ from those obtained in the out-patients.

Table II shows the blood-sugar curves obtained together with the basal metabolic rate. The blood-sugar findings are recorded as milligrams of glucose per 100 c.c. of blood. The basal metabolic rates were taken within forty-eight hours of the sugar tolerance test. The age of the patient and the estimated length of history is also given and the results of urine examination are given in thirteen cases. It is impossible to dogmatize about the length of history owing to the insidious nature of the onset of this disease, and the figures must be accepted as approximate only. It was thought of interest to see if any relationship between the length of history, the severity of the condition clinically, and the results given by estimating the basal metabolic rate and the sugar tolerance could be determined.

It will be seen that the fasting level varied from 65 mg. to 123 mg. with an average of 102 mg. Macleod (10), in his analyses of recorded blood-sugar estimations, gives the normal fasting level as varying from 85 to 110 mg., and it will be observed that all our cases fall within these levels with the exception of Case 6, which shows definite hypoglycaemia, and Cases 7 and 12, where a fasting hyperglycaemia was present. It follows that the fasting level of the blood-sugar cannot be used as a method of determining the existence of acquired hypo-function of the thyroid gland. A general survey of the figures shows that the curve tends to be higher and the fall in the blood-sugar curve to be more prolonged than in healthy individuals; in fact, it does not differ from the curves seen in our cases of exophthalmic goitre. At the end of half an hour the blood-sugar had risen to an average value of 170 mg., with the extremes 211 mg. and 134 mg. With the exception of Cases 1 and 7 the rise was continued at the end of one hour, the average reading being 187 mg., varying from 172 mg. to 214 mg. One and a half hours after the glucose meal the average blood-sugar reading was still 170 mg. With the exception of Case 10, the level of blood-sugar at the end of two hours was higher than the fasting level. The highest reading recorded from these cases was 228 mg. obtained in the one and a half hourly reading in Case 14.

Two urinary specimens could not be obtained; of the thirteen tested, two showed a trace of reduction. Case 14 had no glycosuria, although as stated the blood-sugar reached a level of 228 mg. per 100 c.c. of blood. It is suggested that



the renal threshold is raised in nearly every case of myxoedema, and in this respect differs from exophthalmic goitre, where most observers have noticed a tendency to glycosuria in the majority of cases. Text-books of medicine usually state that the carbohydrate tolerance of myxoedematous patients is increased. Some confusion has arisen in the past by the use of the term increased carbohydrate tolerance when this has been determined by the presence or absence of sugar in the urine after the patient has taken certain quantities of glucose.

Table II shows that when carbohydrate tolerance is estimated by the examination of the blood-sugar after glucose has been given that myxoedematous patients have a definite decreased carbohydrate tolerance.

The basal metabolic rates were obtained by the method of indirect calorimetry described by Cathcart, and varied between  $-14.3$  per cent. and  $-53.7$  per cent. No definite relationship could be demonstrated between the basal metabolic rate and the blood-sugar curve. The lowest rate, i.e.  $-53.7$  per cent., was obtained in the one patient who showed definite hypoglycaemia, but, on the other hand, the same fasting level of 91 mg. was seen in a patient who had a rate of  $-40.8$  per cent., and in another with a reading of  $-14.3$  per cent. The basal metabolic rate did not appear to bear any relationship either to the height of the blood-sugar curve or to the extent to which it was prolonged. The highest two-hourly reading occurred in a case (14) with a rate of 28 per cent., and the lowest 16.7 per cent.

Table II also shows that the probable duration of illness gives no clue to the basal metabolic rate or to the blood-sugar finding. Cases 6 and 7 may be taken as examples, for in both symptoms had been gradually becoming marked over a period of several years—three, or perhaps four, years being given as the date of the probable onset. On clinical examination both cases were classed as very advanced, yet one gave a basal metabolic rate of  $-53$  per cent., and the other of  $-22$  per cent. In Case 6 the hypoglycaemia found contrasts with the fasting level of 123 mg. in Case 7.

The highest curve, the lowest curve, and a composite curve obtained by averaging the figures of Table II are shown in Graph A, together with MacLean's normal blood-sugar curve.

#### *Blood-sugar Curves in Treated Cases.*

Langdon Brown (11) has reported a case of myxoedema treated with thyroid extract which was showing a glycosuria, and quotes Garrod, who found four out of eleven treated myxoedema cases were passing sugar in the urine. Observations of the effect of thyroid extract on the blood-sugar curves in myxoedematous patients do not appear to have been recorded in many cases.

A typical case not shown in Table II may be given. Mrs. H., seen a year previously with marked myxoedema, then had a basal metabolic rate of  $-27.7$  per cent. She was treated with thyroid extract for twelve months and the clinical symptoms disappeared, whilst the basal metabolic rate was altered to  $+18.3$  per

cent. A blood-sugar curve at this stage, after determining a fasting level of 102 mg., gave the following half-hourly readings: 128 mg., 188 mg., 201 mg., and 185 mg.; the urine at the end of the test reduced Fehling. The amount of thyroid was reduced without any return of the symptoms, and whilst still taking thyroid, after an interval of a further six months the fasting blood-sugar was found to be 87 mg., and after glucose was given half-hourly readings showed the following figures: 179 mg., 191 mg., 177 mg., and 118 mg., there being now no glycosuria.

All our cases were treated with thyroid in doses starting from a quarter of a grain each night up to nine grains in the day. We have been able to investigate in some of these cases the immediate and later effects on their sugar tolerance. It was not possible to obtain curves from all our cases, as many of the patients were unwilling to submit to further investigation. Nine cases are tabulated in Table III to show the effect of treatment by thyroid extract on cases of myxoedema. The first reading in each case corresponds to the reading already shown in Table II, before any thyroid treatment has been started.

The immediate effect of giving thyroid extract does not appear to modify the fasting level in the blood-sugar greatly. In two cases a slightly higher level is produced, in two others there is a slight lowering to normal where the original reading had been high, but in five there is no change beyond the normal range.

A general survey of the figures of the treated cases shows that the ultimate effect in the majority of cases is to produce a lowering of the already too high curve and a decrease of the prolongation of the curve which we have described as typical in cases of myxoedema. In three of the cases in Table III the blood-sugar tended to reach a higher level than it had done before treatment, and it will be seen that in four cases glycosuria was found. We have formed the impression that the appearance of sugar in the urine in a case of myxoedema under treatment with thyroid extract is an indication to reduce the dose. In every one of the treated cases it will be seen that the prolongation of the curve is not so marked; the average reading at the end of two hours in eight treated cases of myxoedema was 116 mg. as compared with their original two-hourly reading before treatment of 163 mg.

We found that the carbohydrate tolerance tests as estimated by the blood-sugar curve after the ingestion of 50 grm. of glucose did not give any considerable help in controlling the treatment of myxoedema. We think that where a high curve is further heightened by the giving of thyroid the dose of thyroid extract should be reduced. Improvement in the clinical condition and alteration of a basal metabolic rate from a minus quantity to within normal limits of plus or minus 10 per cent. is a very much safer guide in treatment than any results of a carbohydrate tolerance test. Graphs B and C show the blood-sugar curves obtained before and after treatment in two of the cases quoted in Table III.

*Conclusions.*

1. Severe cases of exophthalmic goitre tend to have high and prolonged blood-sugar curves and to have glycosuria.

2. Myxoedematous patients also give a blood-sugar curve which is higher and more prolonged than in normal persons. There is rarely glycosuria, and it is suggested that the renal threshold is raised in this condition.

3. The fasting level of blood-sugar is in the majority of myxoedema cases within normal limits.

4. No relationship between length of history of symptoms, clinical signs, the basal metabolic rate, and the carbohydrate tolerance test could be established.

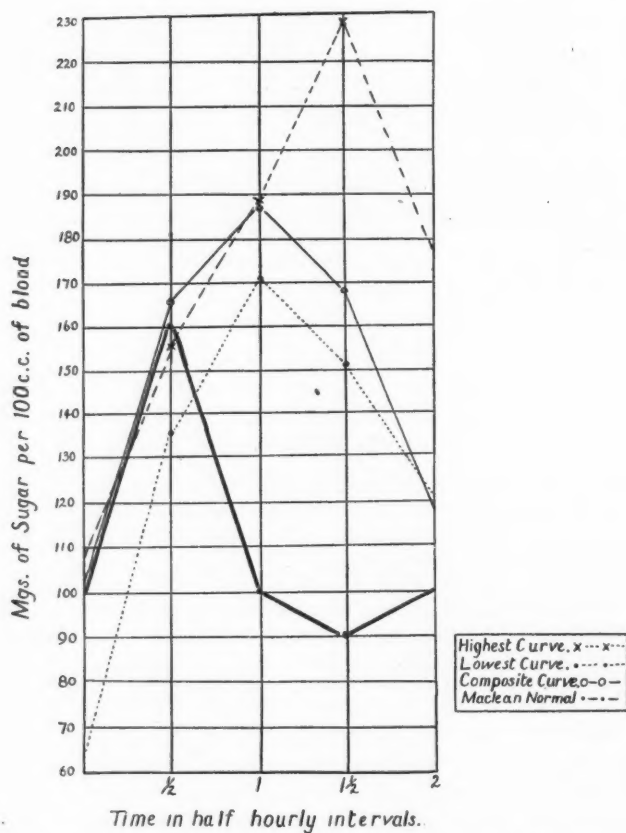
5. Thyroid extract does not raise the fasting level when myxoedematous patients are treated; its general effect is to lower the blood-sugar and to quicken the curve.

6. The carbohydrate tolerance test is not so efficient a method of controlling the treatment of myxoedematous patients as is the determination of the basal metabolic rate.

## REFERENCES.

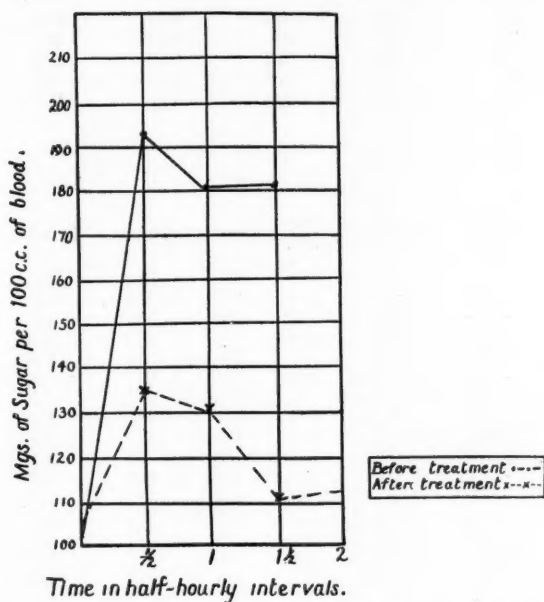
1. Dennis and Aub, *Arch. Int. Med.*, Chicago, 1917, xx. 621.
2. Morris, *Journ. Amer. Med. Assoc.*, Chicago, 1921, lxxvi. 1566.
3. Hamman and Hirschmann, *Arch. Int. Med.*, Chicago, 1917, xx. 761.
4. Janney and Isaacson, *ibid.*, Chicago, 1918, xxii. 160.
5. Sanger and Hun, *ibid.*, Chicago, 1922, xxx. 397.
6. Flesch, *Beitr. für Klin. Chir.*, Tübingen, 1912-13, lxxxii. 236.
7. Geyelin, *Arch. Int. Med.*, Chicago, 1915, i. 16.
8. Grey, *ibid.*, Chicago, 1923, xxxi. 256.
9. MacLean, H., *Glycosuria and Diabetes*, Lond., 1922.
10. Macleod, *Physiol. Rev.*, 1921, i. 208.
11. Langdon Brown, *Lancet*, 1924, i, No 2.

GRAPH A.



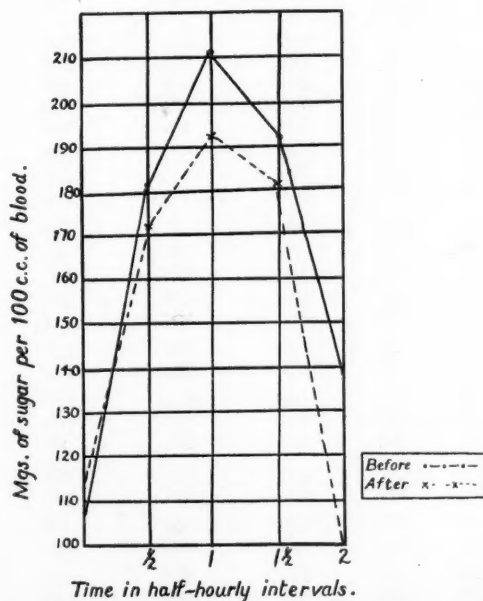
Showing the highest curve, the lowest curve, and a composite curve obtained by averaging the figures of Table II together with Maclean's normal blood-sugar curve.

GRAPH B.



Showing blood-sugar curves before and after 9½ months' treatment in Case F. H. (Table III).

GRAPH C



Showing blood-sugar curves before and after 4 months' treatment in Case F. G. (Table III).

TABLE I

Case.	Fasting.	$\frac{1}{2}$ hour.	1 hour.	$1\frac{1}{2}$ hours.	2 hours.	Urine.
	mg.	mg.	mg.	mg.	mg.	
A. H.	123	157	157	229	201	Reduced
M. G.	109	214	211	172	133	Reduced
E. O.	125	174	179	189	204	Reduced
E. F.	157	194	209	197	204	Reduced

TABLE II

Case.	Age.	B.M.R. %	History.	Fast- ing.	$\frac{1}{2}$ hour.	1 hour.	$1\frac{1}{2}$ hours.	2 hours.	Urine.
				mg.	mg.	mg.	mg.	mg.	
1. L. H.	45	-35	1 yr.	115	201	192	175	—	Trace
2. E. R.	40	-37.5	1 yr.	102	194	181	181	—	None
3. Edith J.	56	-22.9	3 yrs.	114	134	174	136	134	Not tested
4. A. D.	49	-26.7	2 yrs.	85	168	214	133	119	None
5. F. Y.	52	-20.3	7 mths.	109	181	211	194	139	None
6. M. E.	56	-53.7	Several yrs.	65	136	172	152	121	None
7. M. D.	53	-22.8	3-4 yrs.	123	211	188	150	123	Trace
8. M. B.	50	-15	3 yrs.	111	169	172	181	169	None
9. Mary D.	51	-16.1	—	104	165	176	178	134	None
10. F. A.	49	-16.7	3 yrs.	98	181	206	147	96	None
11. A. B.	49	-30	2 yrs.	93	142	181	179	152	None
12. Mary R.	40	-21.1	6 mths.	122	178	197	169	156	None
13. M. R.	34	-40.8	6 mths.	91	137	175	154	129	Not tested
14. A. R.	60	-28	11 mths.	109	156	188	228	179	None
15. E. J.	60	-14.3	6 mths.	91	147	179	147	131	None

TABLE III.

Case.	B.M.R. %	Date.	Fast- ing Level.	$\frac{1}{2}$ hour.	1 hour.	$1\frac{1}{2}$ hours.	2 hours.	Urine.
				mg.	mg.	mg.	mg.	
F. H.	-37.5	22.9.23	102	194	181	181	—	No reduction
	+ 8.3	14.1.24	82	125	164	164	125	" "
		3.3.24	95	152	152	122	116	" "
		2.7.24	106	135	131	112	113	" "
A. D.	-26.7	22.11.23	85	168	214	133	119	No reduction
		8.12.23	128	179	240	170	144	" "
		4.3.24	118	168	147	114	82	" "
F. G.	-20.3	29.11.23	109	181	211	194	139	No reduction
		28.1.24	111	142	162	135	98	" "
		4.4.24	114	172	192	181	100	Trace
M. B.	-15	23.4.23	111	169	172	181	169	No reduction
	+ 5	31.5.23	102	198	217	187	142	Trace
A. B.	-30	9.4.24	93	142	181	179	152	No reduction
		25.4.24	91	175	224	197	152	Trace
F. A.	—	4.3.24	98	181	206	147	96	No reduction
		6.5.24	114	159	160	109	110	" "
		1.7.24	98	129	162	98	81	" "
G. S.	—	14.3.24	137	256	268	242	242	Trace
		28.7.24	114	159	197	201	141	"
M. R.	—	16.4.23	123	178	197	169	156	No reduction
		20.6.24	118	175	188	142	118	" "
G. J.	—	2.5.24	91	147	179	147	131	No reduction
		24.7.24	103	209	169	142	109	" "







## FOUR CASES OF CONGENITAL DEXTROCARDIA, INCLUDING A CASE WITH SINO-AURICULAR BLOCK<sup>1</sup>

By LEONARD ABRAHAMSON

(From the Electro-cardiograph Department, Mercer's Hospital, Dublin)

With Plates 14-16

CONGENITAL dextrocardia shows two varieties, one in which the anomaly is accompanied by transposition of the viscera ('situs inversus'), another in which the transposition is limited to the heart and aorta. Congenital dextrocardia with complete transposition has been known since the seventeenth century, when it was noted anatomically by Riolo (1). Schelenz (2) succeeded in 1903 in collecting 210 observations in the literature. Laubry and Pezzi (3) were able in 1921 to bring the number to at least 227. A close survey of the literature would no doubt add appreciably to this figure. Many observations have probably escaped detection. Isolated dextrocardia is, on the other hand, a rare anomaly. Only 60 cases have been described in the literature, and of these but 29 were authenticated by anatomical findings (4).

In 'situs inversus' the heart is not only situated on the right, but its cavities are transposed, the right auricle and ventricle being on the left, the left auricle and ventricle on the right. The vessels are also transposed. The heart offers thus a mirror image except that such an image would still show the pulmonary artery in a position anterior to the aorta. The transposition of the viscera may be more or less complete. It may implicate the stomach, spleen, liver, intestines, even the lungs, the right lung showing two lobes. In most cases the heart is completely normal, in others congenital anomalies have been found.

The cause of transposition of the viscera is obscure. Most of the theories advanced are as fantastic as they are ingenious. The most simple explanation of congenital dextrocardia is that offered by Abbott (5), who assumes that the embryo lies in an abnormal position within the chorion so that its right side instead of its left is close to the blood-supply. As a result the primitive cardiac tube bends into a contrasigmoid (2) instead of the normal sigmoid (S), and dextrocardia ensues.

<sup>1</sup> Received April 2, 1925.

The diagnosis of congenital dextrocardia may be made by clinical evidence, by X-ray findings, and by electro-cardiography. The electro-cardiograms of the condition are both interesting and instructive. The first observations were made in 1889 by Waller (6), who investigated two cases of transposition and came to the conclusion that the usual electrical relationships were reversed. In 1911 Nicolai (7) published diagrams of tracings from four cases. Another case was published in the same year by Hoke (8). Since then electro-cardiograms of the condition have been published by many observers, including Owen (9), Lewis (10), Neubof (11), Hoffmann (12), Hart (13), Willius (14), Laubry and Pezzi (15), Price (16), Wallace Jones (17).

The electro-cardiograms bear out what one would anticipate theoretically. Lead I, which is the right arm to left arm lead in the normal subject, represents in the dextrocardiac a left arm to right arm lead. In other words, we find in dextrocardia the same tracing in lead I that would be produced in a normal subject by interchanging the arm electrodes. Such a tracing shows inversion of all the waves. In leads II and III, on the other hand, the waves remain upright. The reason for this is that these leads are not symmetric and the course taken by the excitation wave is similar in the dextrocardiac to that taken in the normal subject. One difference there is, and it lies in an interchange between lead II and III. Thus the right arm to left leg lead in the normal subject becomes equivalent in the dextrocardiac to a lead from left arm to left leg, and vice versa.

*Case I.* J. C., male, aged 20, was admitted to Mercer's Hospital on 28.5.23 complaining of discoloration of the skin and conjunctiva. He was seen just after admission by the house surgeon, Dr. M. S. Abrahamson, who noted that the patient was dextrocardiac. The discoloration was found to be due to a medium jaundice of the 'catarrhal' type. The urine contained bile-pigment, the faeces were moderately discoloured. The jaundice steadily cleared up and disappeared completely in a fortnight.

*Family history.* Three sisters, one brother. All normal. Parents alive and normal. No history of congenital dextrocardia in any relative.

*Previous illnesses.* Bronchitis eight months prior to admission. Occasional attacks of 'biliousness', following carbohydrates.

*Examination.* Patient was well built and of a sallow complexion even when the jaundice had disappeared. Tonsils enlarged. Pulse 68. From time to time extra-systoles were noted. Blood-pressure: 120 systolic, 80 diastolic.

The apex-beat was found in the right fifth intercostal space three and a half inches from the mid-sternal line. It was normal in strength and extent. Cardiac dullness was elicited over the right chest and was normal in size and outline. Auscultation revealed normal heart-sounds, heard over the right chest.

Below the lower level of cardiac dullness a tympanitic note was found. Liver dullness was elicited on the left side.

Dr. T. G. Hardman examined the patient by X-rays and reported a dextrocardia with transposition of the abdominal viscera.

*Electro-cardiograms.* The first tracing (Pl. 14, Fig. 1 a) shows inversion of all the waves in lead I, whilst in leads II and III the waves are upright. The 'R' wave is highest in lead III. There is some slight sinus irregularity. The 'T' wave in lead III is unusually large.

Before taking the second tracing (Fig. 1 b) the arm electrodes were inter-

changed, the right arm being brought into contact with the left electrode, the left arm with the right electrode. The tracing shows upright waves in lead I as in the other leads. Lead II is now equivalent to lead III in the previous tracing. There is one ventricular extra-systole ('V.S.').

*Case II.* J. C., aged 52, male, was examined by me in the electrocardiograph department of Mercer's Hospital on 6.2.22 and on 11.2.23. I owed the opportunity of seeing him to the courtesy of Dr. E. Lennon, who kindly permitted me to report his case with my own.

*Family history.* The patient was married. He had one child, a girl aged 21. As far as he knew there was no history of dextrocardia in any of his relatives.

*Previous illnesses.* Pains and stiffness in the joints, mainly of the knees, ankles, and hands. This had troubled him for some years. He had been free from all other illness or complaint.

*Examination.* The patient was a well-built man. Pulse 72. Blood-pressure read 160 systolic, 105 diastolic.

A forcible apex-beat was found in the right fifth intercostal space maximal  $\frac{1}{4}$  inch to the right of the right nipple line. Cardiac dullness was elicited over the right chest, the right border of dullness reaching from  $\frac{1}{2}$  inch to  $\frac{3}{4}$  inch to the right of the nipple line. On auscultation: the first sound in the mitral area was reduplicated; a systolic murmur of medium intensity and an accentuated second sound were heard over the second left intercostal space close to the sternum.

A tympanitic note was found on the right side below the cardiac dullness; liver dullness was elicited on the left side.

I was informed by Dr. T. J. Lane that an X-ray examination undertaken by him at the Meath Hospital showed a dextrocardia with transposition of the abdominal viscera.

*Electro-cardiograms.* The first tracing (Fig. 2 a) shows inversion of 'P' and 'R' waves in lead I. The 'T' wave, which is not seen clearly in this tracing, was seen distinctly in other tracings and was definitely inverted. Lead II and lead III show upright 'P' and 'T' waves. A third wave, which we take to be an 'S' wave, points in a normal downward direction. The 'PR' interval measures  $\frac{1}{2}$  second.

There is left-sided preponderance and sinus irregularity.

The second tracing (Pl. 15, Fig. 2 b) was taken after an interchange had been effected between the arm electrodes. The waves in lead I are now upright. Lead II in this tracing corresponds to lead III in the previous tracing.

*Case III.* E. R., aged 43, female, was referred to the electro-cardiograph department of Mercer's Hospital on 1.7.24 by Dr. P. T. O'Farrell, who very kindly handed over the case to me for further investigation.

*Family history.* The patient was married and had had thirteen children, of whom nine died at an early age. Her mother died of heart disease.

*Previous illnesses.* She had had several attacks of gastric trouble, also two attacks of pleurisy six or seven years ago. She had an attack of erysipelas three years ago. When she was nine years of age she complained of pain in the right praecordium, and was found on examination to have dextrocardia. She had had many similar attacks since. On one occasion she developed a sort of fit and became unconscious.

*Present illness.* She complained of pain referred to the right praecordium. This pain came on at varying intervals, sometimes remaining away for a month, often occurring more frequently. It lasted for an hour or more and radiated to the back. She also complained of attacks of palpitation, with or without exertion.

*Examination.* The pulse was slow, varying in rate from 42 to 60 beats per minute. It was interrupted by frequent pauses, occurring at irregular intervals. Blood-pressure: 190 systolic, 90 diastolic.

The apex-beat was found in the fifth intercostal space, in the nipple line. Cardiac dullness was elicited over the right chest and extended as far as the right nipple line. On auscultation: a soft systolic murmur was audible over the region of the apex-beat. Frequent pauses were noted.

Liver dullness was found on the left side, gastric tympany on the right side. An X-ray examination carried out by Dr. T. G. Hardman showed dextrocardia with complete transposition.

*Electro-cardiograms.* The first tracing (Fig. 3 a) shows inversion of all the waves in lead I, whilst in leads II and III the waves are upright. There is some sinus irregularity, and in lead I two long pauses are seen.

The second tracing (Fig. 3 b) demonstrates a long pause which measures slightly less than twice the succeeding cycle. This pause is due to the presence of sino-auricular block.

*Case IV.* T. J. O'B., aged 43, male, attended at Mercer's Hospital for an injury to the right arm.

*Family history.* The patient was married and had five healthy children.

*Previous illnesses.* Negative.

*Present condition.* Suffered from 'rheumatic' pains in the shoulders. There was no complaint whatever referable to the heart.

*Examination.* Pulse 72. Blood-pressure: 130 systolic, 80 diastolic.

The apex-beat was found in the fifth right intercostal space inside the nipple line. Cardiac dullness was normal, but was elicited over the right chest. The heart-sounds were heard best over the right side.

Liver dullness was found on the left side, gastric tympany on the right side.

*Electro-cardiograms.* The first tracing (Pl. 16, Fig. 4 a) shows inversion of the 'R' and 'T' waves in lead I. The 'P' wave is not seen. In lead II, which is not shown in this tracing, and in lead III the 'R' and 'T' waves are upright, whilst the 'P' wave is inverted.

The second tracing (Fig. 4 b) was taken after an interchange of the arm electrodes. The 'R' and 'T' waves are upright in all leads, the 'P' wave inverted in leads II and III. Lead II in this tracing corresponds to lead III in the previous tracing.

#### REFERENCES.

1. Rioloano, quoted by Otto in *Seltene Beobachtungen zur Anatomie, Physiologie und Pathologie*, 1816.
2. Schelenz, *Berl. klin. Woch.*, 1909, xvi. 788 and 840.
3. Laubry et Pezzi, *Traité des Maladies Congénitales du Cœur*, 1921, 269.
4. Idem, *ibid.*, 279.
5. Abbott, M. E., 'Congenital Cardiac Disease', in *Mod. Med.*, Philad., Lippincott, 1908, iv. 323-445.
6. Waller, *Phil. Trans. Roy. Soc., Lond.*, 1889, clxxx. B. 169.
7. Nicolai, *Berl. klin. Woch.*, 1911, xlviii. i. 51.
8. Hoke, *Munch. med. Woch.*, 1911, lviii. i. 802.
9. Owen, *Heart*, Lond., 1911-12, iii. 113.
10. Lewis, *Brit. Med. Journ.*, 1912, i. 1422.
11. Neuhof, *Journ. Amer. Med. Assoc.*, Chicago, 1913, ix. 1064.
12. Hoffmann, *Die Elektrokardiographie*, Wiesbaden, 1914, 71.
13. Hart, *The Diagnosis and Treatment of Abnormalities of Myocardial Function*, New York, 1917, 237.
14. Willius, *Clinical Electrocardiography*, 1922, 141.
15. Laubry et Pezzi, *Traité des Maladies congénitales du Cœur*, 1921, 278.
16. Price, F. W., *Diseases of the Heart*, Oxford, 1918, 434.
17. H. Wallace Jones, H., *Brit. Med. Journ.*, 1924, i. 147.



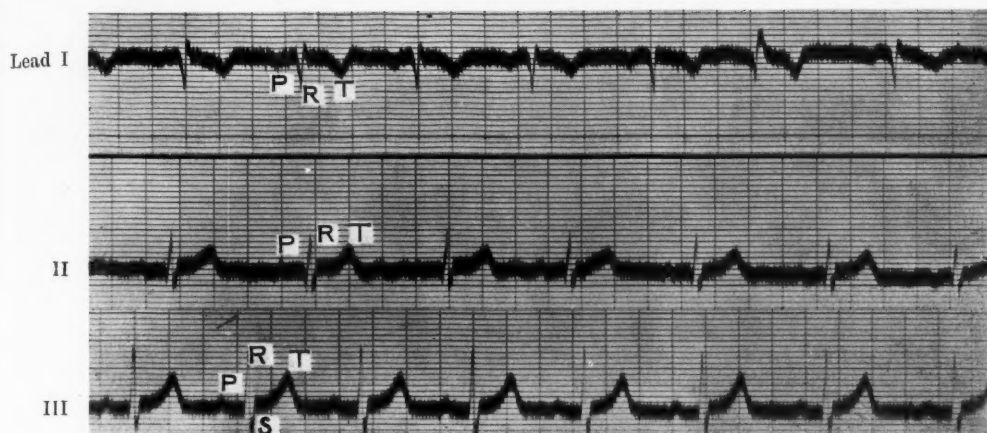


FIG. 1 a. Showing inversion of waves in lead I

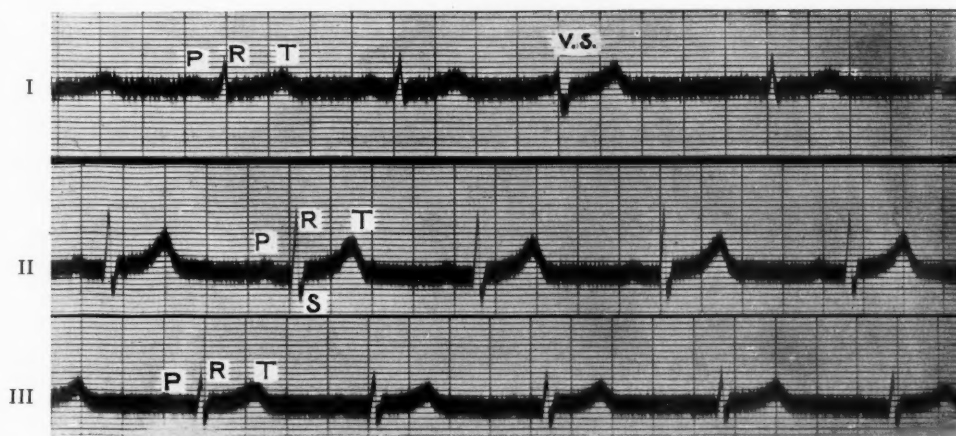


FIG. 1 b. Shows effect of interchange of arm-electrodes

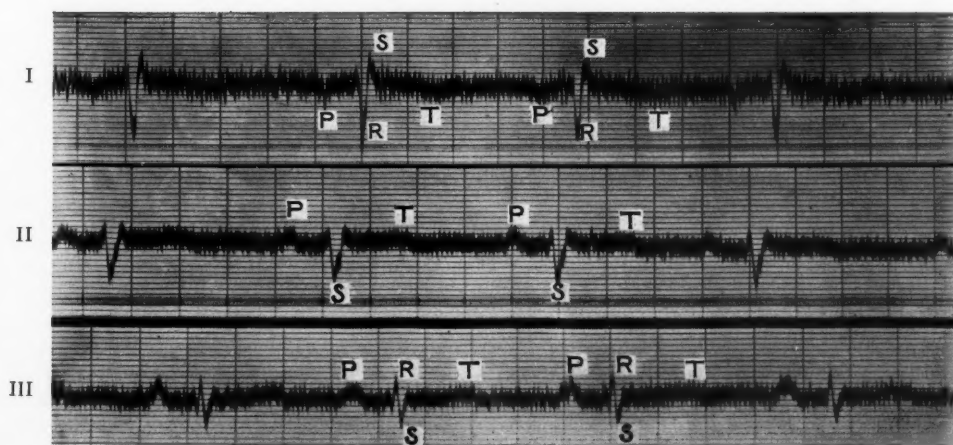


FIG. 2 a. Inversion of waves in lead I



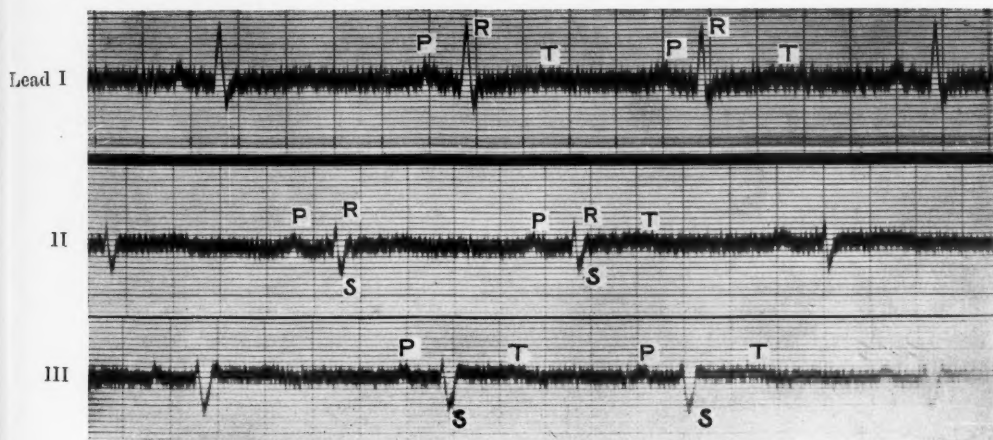


FIG. 2b. Interchange of arm-electrodes

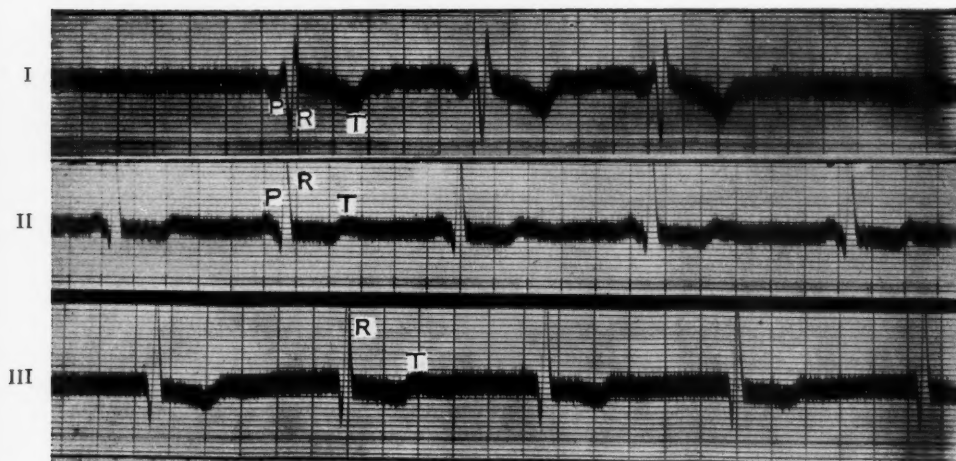


FIG. 3a. Inversion of waves in lead I with two long pauses

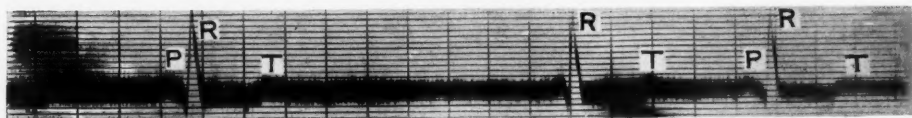


FIG. 3b. Long pause due to sino-auricular block



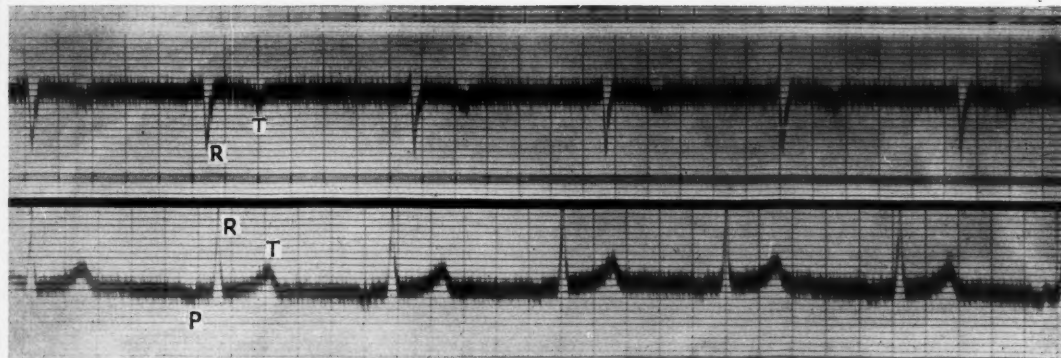


FIG. 4a. Inversion of 'R' and 'T' waves in lead I

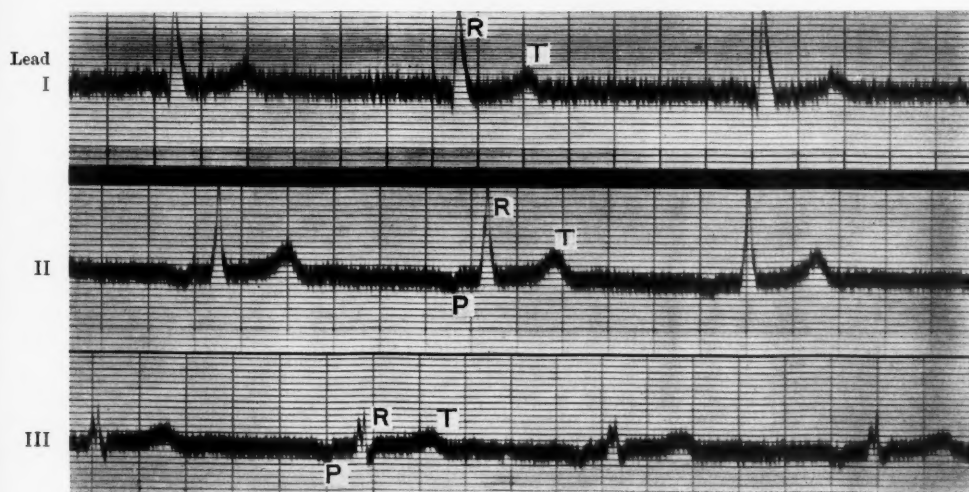


FIG. 4b. Interchange of arm-electrodes

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n



ACUTE ILEOCOLITIS IN CHILDREN<sup>1</sup>

BY ROBERT CRUICKSHANK

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THE classification of acute diarrhoea in children has, in the past, afforded considerable difficulty to paediatrists; the main reason for this is that the causal factors have not yet been definitely established. At present, classifications are based on (a) clinical phenomena, (b) pathological and post-mortem appearances, (c) the bacteriological study of the stools, (d) the chemical character of the dietary, and the result is a great confusion of nomenclature, and a labelling of similar types of diarrhoea under different terms. Both Hutchison and Still classify their cases according to the severity of the diarrhoea, that is, on clinical data, and recognize (1) simple diarrhoea (intestinal catarrh, intestinal dyspepsia), (2) febrile diarrhoea (acute gastro-enteritis, summer diarrhoea, ileocolitis), and (3) cholera infantum (a more severe form of (2)). Thomson believes that such a classification, or one based on pathological findings—such as (1) gastro-enteritis, (2) follicular enteritis, (3) colitis—is unsatisfactory, and he adopts the teaching of the German paediatrists Finkelstein and Czerny and Keller, who attribute most forms of gastro-intestinal upset to a chemical fault in the dietary. According to the severity of the upset, the disease is named (1) *Bilanzstörung* (disturbance of equilibrium), (2) *Dyspepsie*, (3) *Decomposition*, (4) *Intoxication*, and the last of these includes febrile dyspepsia, intestinal catarrh, summer diarrhoea, and cholera infantum. This school also recognizes an infective gastro-enteritis, due to invading micro-organisms, e.g. *Streptococcus enteritidis*, *B. proteus*, dysentery bacilli, and *B. welchii*, but states that no clinical differentiation corresponding with the bacteriological findings is possible. Talbot and Morse likewise classify all forms of 'infective gastro-enteritis' together, but consider them apart from the simple or fermentative diarrhoeas. Koplik follows the teaching of Escherich and his pupils, and divides diarrhoeas into (1) those resulting from mechanical irritation, and (2) those of infective origin, in which the infecting organism may be either endogenous (already in the bowel), or ectogenous (an invading organism not normally present in the bowel).

In a bacteriological investigation of the intestinal flora of children suffering

<sup>1</sup> Received May 1, 1925.

<sup>2</sup> This work was done during the tenure of an Anderson Fellowship (Aberdeen).

from acute diarrhoea, a classification on purely clinical grounds suggested by Professor Leonard Findlay was adopted, viz.: (1) intestinal dyspepsia (simple diarrhoea without fever or toxic phenomena); (2) gastro-enteritis, accompanied by fever and symptoms of intoxication: this latter group includes all cases of summer diarrhoea, and cholera infantum; (3) ileocolitis, accompanied by fever and toxic symptoms, but differing from (2) in that the stools are mucoid in character, and contain blood and pus.

It is with the third group—acute ileocolitis—that the present investigation is concerned. This form of diarrhoea may be defined as an acute infection which attacks the greater part of the large bowel and the lower end of the small intestine, causing a catarrhal inflammation with the consequent passage of mucoid stools containing blood and pus; in severe cases the condition may go on to coagulation-necrosis of the mucous membrane. Clinically, the disease is indistinguishable from bacillary dysentery, but the fact that in this country it occurs sporadically, and not in epidemic form, seems to have obscured the possible aetiological relationship of the dysentery bacillus. In America, acute ileocolitis is grouped with other acute diarrhoeas under the generic term summer (or epidemic) diarrhoea; and the value of many of the bacteriological studies by American workers is diminished because they do not differentiate between gastro-enteritis and ileocolitis. The latter type of diarrhoea is much more prevalent in America than it is in this country, and forms a large percentage of the cases of epidemic enteritis occurring during the summer season. In Britain, although the sporadic occurrence of diarrhoea characterized by the passage of slimy stools containing blood and pus has been generally recognized, little attempt has been made to prove or disprove the aetiological connexion of *B. dysenteriae* with cases of this type. It is interesting, however, to find Nabarro (22) stating at the meeting of the British Medical Association in 1923, in his paper on 'Summer Diarrhoea': 'I have no doubt, from my eleven years' experience at Great Ormond Street, that infections due to *B. dysenteriae* have been much more commonly met with in children since the war than in pre-war days.'

During the year 1923-24, the stools of ten cases at the Royal Hospital for Sick Children, Glasgow, and two other cases of acute ileocolitis have been examined bacteriologically. A brief clinical survey of the hospital cases, and the results of the bacteriological findings in all the cases, are given.

#### *Clinical Notes.*

The cases occurred sporadically at all seasons. Only four of the patients were admitted during the months of July, August, and September when summer diarrhoea is most prevalent. Although most of the cases were from the poorer quarters of the city, no special district was affected. In only one instance was there a possibility of infection from one case to another. A child (A. W., aged 1½ years) was admitted to hospital on 15.9.23, suffering from purpura haemorrhagica, and did well; on 2.10.23 (seventeen days later), another child (M. C.,

1 $\frac{1}{2}$  years), suffering from ileocolitis, was admitted to the same ward, and two days later A. W. developed diarrhoea with blood and pus in the motions. No likely source of infection other than the child M. C. was discovered. It is significant, too, that in one case the mother, and in another case the father, had a sudden attack of diarrhoea at the same time as the child. Special inquiry was made in six of the ten hospital cases, as to whether the father had been abroad or had suffered from dysentery, but a negative reply was given in every instance.

Five of the ten hospital cases suffered from diarrhoea of a chronic type previous to, and in the majority of the cases immediately preceding, the onset of the ileocolitis. This fact may have some aetiological significance, since the previous diarrhoea possibly caused a lowering of resistance of the bowel to infection.

*Age.* One of the cases was under one year of age, five were between one and two years, and the remaining six were from two to ten years old. Koplik gives the second year of life as the age of greatest incidence.

*Sex.* Seven were boys, and five were girls.

*Food.* In no case did the onset of symptoms have any relation to the taking of any special article of diet. There was nothing abnormal about the previous feeding. The infant under one year of age had been artificially fed.

*Symptomatology. Onset.* The illness commenced with diarrhoea in every case, either sudden in onset or, if present for some time previously, it was followed by the passage of slimy stools containing blood and pus and accompanied by fever. Vomiting was present at the onset in four of the cases. One child was admitted in an unconscious state, and had convulsions both before and after admission.

*Condition on admission.* The children, as a rule, looked ill when admitted, and showed evidence of intoxication by the anxious sunken eyes and drawn expression of the face, furred tongue, dry pungent skin, and often a smell of acetone in the breath. In only two cases, however, was there marked water depletion of the tissues with loss of elasticity of the skin; the other children were moderately well nourished, and did not present the dehydrated appearance of the typical case of acute gastro-enteritis. Abdominal tenderness was elicited in one case. Fever was present in every case on admission. There was nothing abnormal to be made out on general physical examination.

*Faeces.* The motions were small, frequent, and slimy, with a foetid odour, and were composed almost entirely of mucus, blood, and pus. Tenesmus accompanied the bowel movements. Microscopically, in the early stages, a stained film of the faeces showed abundance of red blood cells, polymorphonuclear cells, and macrophages. The latter two types showed phagocytosis of Gram-negative bacilli which were present in practically pure culture during the first days of the illness. The blood, as a rule, disappeared from the stools first, and the motions usually remained slimy for a few days after the disappearance of the pus cells.

*Urine.* Acetone bodies were present in the urine in nine of the ten hospital cases: they were reported as a trace in three of these, and abundant in the remaining six cases (Rothera's test). There was generally a haze of albumin

in the urine for the first few days, and blood and pus cells were found in one specimen.

*Temperature.* During the acute stage of the illness, the temperature varied from 100° to 102° F. in the severer cases, and from 98° to 100° F. in the milder cases. In one child it reached 104° F. In all cases by the end of the first week the temperature had fallen considerably; thereafter it generally subsided to normal as the character of the motions improved. The pulse-rate varied with the temperature. The respirations, in the absence of respiratory complications, were practically normal.

*Blood count.* The white cells were counted in four cases under 2 years, and in each numbered about 12,000, which is normal for children of this age.

*Duration.* The average duration of the illness, that is, until the motions were perfectly normal and remained so, was ten days from the date of admission to hospital, or twelve days from the reported onset of slimy stools with blood and pus.

*Diagnosis.* The diagnosis rests on the passage of a diarrhoeic stool containing mucus, blood, and pus, and accompanied by fever and symptoms of intoxication. Two of the cases were sent in with the diagnosis of intussusception, and this is the condition with which ileocolitis is most likely to be confused. In doubtful cases, an abdominal and rectal examination should be made under an anaesthetic so that a tumour may not be overlooked. The absence of physical signs, the presence of fever, and the demonstration of pus in the stools should be sufficient to distinguish ileocolitis from intussusception.

*Widal reaction.* In two cases the patient's serum was tested against a standardized *B. dysenteriae* (Flexner V) emulsion for the presence of agglutinins. The blood was withdrawn four and seven days respectively after admission, and dilutions of 1:20 and 1:40 of the serum agglutinated the dysentery emulsion. The Widal reaction is of no practical value in the diagnosis of dysentery, because (1) agglutinins do not develop in the blood of the patient as a rule till about the twelfth day of the illness, and (2) normal sera may agglutinate *B. dysenteriae* (Flexner) in dilutions of 1:100 to 1:150. Ritchie (quoted by Stitt) tested the sera of 792 normal persons and found that 41 per cent. of the sera agglutinated Flexner strains of the dysentery bacillus in 1:64, and 30 per cent. in 1:128.

*Prognosis.* In the present series not one of the patients died of the ileocolitis *per se*. Of the twelve cases, one died, a premature twin who developed broncho-pneumonia during the convalescent stage of the ileocolitis. At autopsy, hyperaemia of the mucosa of the colon was found, together with some catarrh: there was marked focal fatty change in the liver, similar to what is frequently found in fatal cases of gastro-enteritis. One case developed whooping-cough, and another measles, during convalescence, and these were transferred to the Fever Hospital. The others were all discharged well. Of the thirteen cases of Dr. Nabarro, from which dysentery bacilli were isolated, three died. Koplik gives the mortality as being 30 to 40 per cent.

*Treatment.* On admission each child had the routine rectal wash-out, *plus*

a dose of castor-oil, and only water was given during the first twelve to twenty-four hours. Buttermilk curd mixture, corresponding to Finkelstein's protein milk, was then given, commencing with half an ounce six times a day, and the quantity rapidly increased every day, until the child was getting seven ounces six times a day. When the motions were normal and the weight increasing, whole milk feeding was instituted, and finally a mixed diet suitable for the age of the child was given. In those cases in which acetone bodies were marked in the urine, sodium bicarbonate in large doses was given by mouth in view of possible acidosis. As regards medicinal treatment, all the cases except two received magnesium sulphate in amounts varying from 10 to 30 grains in three successive doses at hourly intervals each morning, and this treatment was continued till the motions were normal. In one case admitted with convulsions, in whom the toxic symptoms were very pronounced, anti-dysentery serum (Flexner-Y type) was given subcutaneously in doses of 10 c.c. twice daily for two days and 10 c.c. on the third day. Although in this case there was marked improvement in the general condition, the motions remained unchanged, so that magnesium sulphate had to be continued. In one case, rectal injections of tannic acid were employed, and in another emetine hydrochloride,  $\frac{1}{4}$  gr. subcutaneously twice a day, but the results were not so satisfactory as with magnesium sulphate. It is suggested, in view of the uniformly good results with this treatment, that in cases of acute ileocolitis, magnesium sulphate should be exhibited in the doses described above, and that in addition antidysentery serum of Flexner-Y type (20-30 c.c. per day) should be employed as a routine from the day of admission to combat the toxic symptoms. Later, when the agglutinability of the isolated organism has been tested with the V, W, X, Y, Z types, the corresponding monovalent serum may be used. Recently, the use of kaolin has been strongly advocated in intestinal infections which are accompanied by marked toxic symptoms, such as cholera and dysentery (Braafladt (6)). Prof. Findlay has already tried it in cases of gastro-enteritis with rather disappointing results, but it is probable that it would be found more beneficial in ileocolitis.

#### *Results of Bacteriological Investigation of the Stools.*

After the discovery of the dysentery bacilli (Shiga, Kruse, Flexner, 1898-1900), the first investigation regarding the relationship of these organisms to infantile diarrhoea was from America by Duval and Bassett (9), who, in 1902, isolated dysentery bacilli from the stools of forty-two out of fifty-three cases of enteritis. In 1903 the Rockefeller Institute (11) carried out an extensive bacteriological examination of the faeces of children suffering from 'summer diarrhoea' in several of the largest towns in America, with the result that dysentery bacilli, mostly of Flexner type, were found in 63 per cent. of 412 cases. Since then many American workers (notably Wollstein (33), Park, Collins and Goodwin (23), Weaver and Tunnicliffe (30), Graham (12)), have isolated organisms of the dysentery group from the stools in cases of epidemic enteritis. In an investigation



into the aetiology of summer diarrhoea in England for the Board of Health (5) (1911-12) by Lewis, Alexander, O'Brien, Graham-Smith, *et alii*, organisms classified as dysentery bacilli were found in the stools of only eight out of 659 cases of diarrhoea. Logan (17) recovered non-agglutinable dysentery bacilli from three out of fourteen cases of enteritis, and Nabarro (22) in a series of 107 cases of enteritis found dysentery organisms in six cases of summer diarrhoea, and in seven cases of 'other types of diarrhoea'.

Morgan (21) has isolated from the stools of cases obviously not suffering from dysentery, such as typhoid carriers, typical mannite-fermenting bacilli, of which 58 per cent. were agglutinable by an antidysentery serum, and the question arises as to whether the bacillus of dysentery may occur as a saprophyte in the healthy intestine. Flexner (11), in reviewing the researches of the Rockefeller Institute (1903), regarded this as possible, but at the time not proven. Dr. Marshall Findlay (10) at Great Ormond Street Dispensary (1923) found organisms of the dysentery group in the faeces of thirteen out of 139 healthy children, but there is no mention as to whether these organisms were agglutinated by an antidysentery serum. Schorer (25), in a bacteriological examination of the stools of a thousand American soldiers returning from France, isolated dysentery bacilli in only two cases. The writer failed to find any dysentery organisms in the faeces of forty healthy children under one year of age, seen at the out-patient department, R. H. S. C., Glasgow, or in the stools of thirty-two cases of gastro-enteritis treated in the wards. Thus dysentery bacilli do not appear to be present to any notable extent in the faeces of children not suffering from ileocolitis as defined here.

#### *Method of Isolation.*

In the present series the stools were examined at periods varying from the first to the seventh day after the onset of diarrhoea. It is necessary to emphasize the importance of examining the faeces (1) as early as possible in the course of the illness, and (2) soon after the specimen has been taken. Dysentery bacilli quickly disappear from the faeces in the course of the disease, and even by the third or fourth day they are present in much smaller numbers than at the beginning of the attack (Mackie (18)). It is essential, too, that cultures of the faeces be made within three or four hours after the specimen has been taken from the bowel, or if not, the glycerin and saline preservative<sup>1</sup> should be used. In taking the specimens the well-known rectal swab and speculum method was employed. A small sterile glass speculum is inserted into the anus, a rectal swab, rather stouter than that used as a throat swab, is passed along the speculum into the rectum, and with a rotatory movement of the swab sufficient faeces are secured to make an emulsion in a test-tube containing 1 c.c. of sterile saline solution (or glycerin and saline). Plates of MacConkey's lactose bile-salt

<sup>1</sup> The faeces are emulsified with about double the volume of 30 per cent. neutral glycerin in 0.6 per cent. NaCl solution (Teague and Clurman (28)).



neutral red medium are stroked from this emulsion and incubated at 37° C. for twenty-four hours. Colonies of the typical dysentery bacilli are usually very small, translucent, and slightly raised, with, as a rule, a regular margin. If no suspicious colonies are seen after twenty-four hours the plates should be incubated for twenty-four hours longer, as occasionally the colonies are not visible till after forty-eight hours' incubation. Non-lactose fermenting colonies of the type described above are subcultured on agar-slopes, on which the typical dysentery bacillus grows as a delicate, whitish, often waxy-like, growth in striking contrast to the heavy growth of atypical and pseudo-dysentery organisms. The cultures are then tested for their cultural reactions (fermentation of sugars, motility, indol-formation, &c.), and for their agglutinability with antidysentery sera. As the organisms tend to die quickly when recently isolated, it is advisable to make subcultures repeatedly at two-day intervals.

#### *Fermentation Reactions.*

Non-lactose fermenting organisms were isolated from eleven of twelve cases examined. The negative case (I. T., aged 7½ years) had had diarrhoea with blood and pus in the motions for six days before admission. Organisms of the Flexner-Y dysentery group were isolated from the faeces of seven of the remaining eleven cases. These seven strains all produced acid, but no gas, in glucose and mannite, and three fermented, in addition, maltose. Indol was formed within twenty-four hours by every strain. Table I shows the sugar reactions after the strains had been repeatedly subcultured.

TABLE I.

Name.	Motility.	Lactose.	Glucose.	Mannitol.	Dulcitol.	Maltose.	Saccharose.	Litmus milk.	Indol.
*J. K.	-	-	A	A	-	A	-	Sl. alk.	+
A. W.	-	-	A	A	-	-	-	Alk.	+
D. L.	-	-	A	A	-	-	-	Sl. alk.	+
W. D.	-	-	A	A	-	A	-	Sl. alk.	+
*C. C.	-	-	A	A	-	A	-	Sl. acid	+
J. M.	-	-	A	A	-	-	-	Alk.	+
T. S.	-	-	A	A	-	-	-	Alk.	+

A = Acid-production.

Alk. = Alkaline reaction in litmus milk.

The sugar reactions were read after 7 days' incubation at 37° C.

\* All the strains were re-tested at varying intervals. The only change noted was that J. K. and C. C. did not ferment maltose when first isolated, but subsequently did so.

#### *Results of Agglutination with Antidysentery Serum.*

All the above strains were tested for agglutinability with a Flexner-Y serum obtained from the Laboratories of the Pathological Department, Oxford, and all were agglutinated to titre. In view of the work of Andrewes and

Inman (1) and others on the serological races of the Flexner-Y group, six of the strains were further tested with the monovalent antisera prepared by the Oxford Standard Laboratories (viz. Types V, W, X, Y, Z), and all were agglutinated by two or more of the antisera. Table II shows the results of agglutination with the monovalent antisera.

TABLE II.

Monovalent antisera to strains—V, W, X, Y, Z.

Name.	V	W	X	Y	Z
J. K.	—	—	1:40	1:40	—
A. W.	—	—	1:40	1:40	1:80
D. L.	—	—	—	1:160	1:40
W. D.	1:20	—	1:40	1:80	—
C. C.	1:20	1:80	—	1:80	—
J. M.	1:20	—	—	1:80	—

— = no agglutination in a dilution of the serum of 1:10.

The figures represent the highest dilution of the antiserum in which agglutination was present. No titre is given with the monovalent antisera supplied by the Oxford Laboratories: 1 c.c. of antiserum is standardized to contain 100 agglutinin units.

The titre of the Flexner-V antiserum when tested with a standardized Flexner-V bacillary emulsion was 1:80.

In carrying out the agglutination tests, 24-hour cultures of the organisms on agar were emulsified in normal saline and heated at 55° C. for half an hour. The emulsion was then added to an equal volume of appropriate dilutions of the antisera, and placed in the water-bath for 4½ hours at 55° C. After the tubes had stood for eighteen hours further at room temperature, readings were made. It is to be noted that the flocculi of dysentery bacilli are much smaller than with the typhoid group of organisms, and consequently the sediment is more granular.

The antiserum which agglutinates most of the strains is that to the original Y strain of Hiss and Russell, and should not be confused with the Y strain of the Pasteur Institute, which is here represented by Type W, while Type V is the original Flexner strain. By comparison of the tables it is seen that the strains which in their fermentative reactions belong to the Y group (non-maltose fermenting) are those which with one exception (A. W.) are most markedly agglutinated by the Y antiserum. Further it is evident from Table II that it is difficult to assign a strain to a particular serological race, since it may be agglutinated equally by two different antisera. Hence for routine clinical diagnosis it is advisable, as has been recommended, to use a polyvalent serum prepared by pooling the five monovalent sera.

#### *Isolation of Organisms other than True Dysentery Bacilli.*

Morgan's I bacillus was isolated from the faeces of two of the remaining four cases on the fourth and sixth days of the illness respectively; and from a third an organism of *B. coli anaerogenes* type was discovered. The latter organism was a motile, Gram-negative bacillus, which formed acid but no gas

from glucose, mannite, maltose, and saccharose, fermented lactose slightly after ten days, and formed indol. It differs from the atypical dysentery bacilli in being motile. It is interesting in this connexion that Nabarro isolated *B. coli anaerogenes* from the faeces of 25 out of 107 cases of gastro-enteritis. A Gram-negative coliform bacillus which produced acid but no gas from glucose and mannite, but failed to form indol after ten days' incubation in peptone water, was isolated from the faeces of the remaining case. This organism was tested for agglutinability with the polyvalent antiserum (Flexner-Y type) and with the five monovalent antisera, but was not agglutinated by any of these. It is a noteworthy fact that this atypical non-agglutinable organism was isolated from the child M. C., while from A. W., who was almost certainly infected from M. C. (see Clinical Notes), a typical agglutinable Flexner bacillus was isolated.

From the cases yielding *B. dysenteriae* at the first examination, a second rectal swab was always taken seven days after the first specimen. The results of these are interesting. Morgan's I bacillus was recovered in scanty numbers from the faeces of two cases; from a third case, a non-motile coliform bacillus producing acid but no gas from glucose, mannite, maltose, and saccharose was isolated; and in another case, examination of the faeces on four occasions during three weeks yielded each time a non-motile bacillus which produced acid but no gas from glucose, mannite, maltose, and dulcitol, and formed indol. None of these atypical strains was agglutinable by any of the antidysentery sera.

Much has been written in recent years upon the atypical dysentery bacilli, isolated chiefly from mild examples of the dysenteric type of diarrhoea (Sonne (27), Thjøtta (29), Mackie (18)). Mackie gives the following as the characteristics of these organisms: they are all non-motile and produce acid without gas from glucose, but they vary as regards fermentation reactions with the other sugars and formation of indol; they are not agglutinated by any of the antidysentery sera. While there is strong evidence of the causal relationship of these organisms to certain cases of dysentery, there can be no doubt that this form of intestinal infection favours the development of concomitant organisms, which are closely related in their cultural reactions to the true dysentery bacilli, and which tend to predominate in the faeces at a later stage of the disease, after the dysentery organisms themselves have disappeared from the faeces. Other organisms such as *B. Morgan I* and variants, *B. faecalis alkaligenes*, and paracolon types, have been isolated in the convalescent stage of dysentery (Mackie).

While, therefore, the possibility of the aetiological relationship of *B. Morgan I* (20), or of the atypical dysentery bacilli, to ileocolitis cannot be denied, in view of the findings it is perhaps more reasonable to regard the atypical organisms isolated in the present series as concomitant organisms, and to attribute the failure to recover true dysentery bacilli from five of the cases to the late stage of the illness at which the stools were examined.

*Discussion regarding the Aetiological Relationship of B. dysenteriae to Ileocolitis.*

Two points merit discussion: (1) Does the dysentery group of organisms cause a specific type of infection which can be readily recognized clinically? (2) Are there organisms other than the dysentery bacilli capable of producing ileocolitis? Regarding the question of the dysentery group of organisms being responsible for a specific and clinically recognizable type of infection, Holt, in reviewing the work of the Rockefeller Institute on summer diarrhoea from the clinical standpoint, gave it as his opinion that infection with the dysentery bacilli is associated with almost every sort of intestinal disturbance accompanied by diarrhoea, and that *B. dysenteriae* is associated with diarrhoeal enteritis of all degrees of severity. Yet the clinical reports show that all but three of the cases from which *B. dysenteriae* was isolated had slimy, mucoid stools, and about one-third of these had blood and pus in their motions. Knox (16) stated that among children diarrhoea due to *B. dysenteriae* cannot be differentiated from ordinary summer diarrhoea, and his conclusions were corroborated by Rotch (24), Hastings (13), and Duval and Bassett (9), all of whom isolated *B. dysenteriae* of Flexner and Shiga types from cases which were not clinically ileocolitis. It is apparent, however, where clinical notes are appended that the great majority of cases yielding dysentery bacilli had slimy stools usually associated with blood and pus. On the other hand, Park, Collins, and Goodwin failed to find *B. dysenteriae* in any case of cholera infantum, but isolated the organism in a large percentage of cases with excessive mucus in the stools. Schwartz (26) examined thirty cases of summer diarrhoea without mucus in the stools and failed to find *B. dysenteriae*. Graham isolated the dysentery bacillus in 63 per cent. of his cases of ileocolitis, but did not recover the organism from other types of diarrhoea. Similar results were reported by Charlton and Jehle (7), and Collins (8). Weaver and Tunnicliffe (30) isolated organisms of the dysentery group from 24 out of 97 cases of ileocolitis, but none from other diarrhoeal cases. In Britain, Morgan (20) (1906) did not think that *B. dysenteriae* was a causal organism in the epidemic enteritis of the summer months. Nabarro isolated *B. dysenteriae* from 13 of his 107 cases, six being from cases of summer diarrhoea and seven from other types of diarrhoea, but no clinical reports are given. It is interesting to note that in Egypt, Whitehead and Kirkpatrick (31), in an examination of the stools of 5,000 soldiers suffering from diarrhoea without blood and pus in the stools, isolated Flexner-Y bacilli from only two cases and Shiga dysentery bacilli from none.

Diarrhoea of a dysenteric type has, on the other hand, been attributed to numerous organisms other than those of the dysentery group. Morgan isolated *B. Morgan I* from the stools of 20 out of 37 children suffering from 'catarrhal diarrhoea'. *B. pyocyaneus* has been isolated by numerous workers (Baker, Wollstein (32), Baginsky (2)) from cases of enteritis and dysentery. Justi (15), in

reviewing the findings of these investigators, concludes that while *B. pyocyaneus* usually occurs in the intestine as a harmless saprophyte, it may nevertheless be a causal agent in infectious diarrhoea. Much the same has been claimed for *B. proteus* (Metchnikoff (19), Bloch (4), Horowitz (14)), although, according to these authors, infection with *B. proteus* causes a gastro-enteritis rather than an ileocolitis. Bahr (3) (Denmark) found *B. proteus* in the stools of only 12 out of 117 typical cases of summer diarrhoea. The Committee of the Medical Research Council (Special Report Series 51) adopts a non-committal attitude in stating that there seems no sufficient evidence that *B. proteus* is a primary cause of enteritis whatever may be its importance as a secondary infective agent. Other organisms which have been claimed as causal factors in diarrhoea of a dysenteric type are *B. welchii*, *B. sporogenes*, and *Streptococcus enteritidis*, but the argument which applies equally against these as against *B. proteus* and *B. pyocyaneus* is that all these organisms are present as harmless saprophytes in a certain percentage of healthy intestines. It may be that under certain conditions of disease a favourable medium for their proliferation is established so that they are present in the intestine in much greater numbers than normally, and they may act in prolonging a diarrhoea already induced by some other agent.

The analysis of the literature as well as the present observations give strong support to the view that where in children there is ileocolitis, i.e. a form of enteritis clinically recognizable through the presence in the faeces of mucus, blood, and true pus (polymorphonuclear leucocytes), dysentery bacilli of the classical type play an important, if not a preponderating, rôle in the causation.

#### *Conclusions and Summary.*

1. Acute ileocolitis in children is characterized clinically by the passage of mucoid stools containing blood and pus, accompanied by fever and symptoms of intoxication. It is a diarrhoeal condition which occurs not so much in infancy as in early childhood.

2. The disease occurs sporadically in this country, and is not limited to any season of the year. A previous diarrhoeal attack would seem to be a predisposing factor in the aetiology.

3. The resemblance of the disease clinically to dysentery suggested that organisms of the dysentery type might be the causal agents. In a bacteriological examination of the stools of twelve cases of acute ileocolitis, *B. dysenteriae* of Flexner-Y type was isolated from seven cases.

4. In the convalescent stage of the illness, atypical dysentery bacilli were isolated from the faeces of four patients, and *B. Morgan I* from the faeces of other four. Since *B. dysenteriae* (Flexner) had been previously isolated from the stools of some of these cases, these types were regarded as concomitant bacilli rather than as the causal organisms.

5. There is no conclusive evidence that organisms other than those of the *B. dysenteriae* group are primary infective agents in producing acute ileo-



colitis, although they may act as secondary factors in prolonging the diarrhoea. *B. dysenteriae*, on the other hand, seems to produce an inflammatory condition of the large intestine and the lower part of the ileum, resulting in a type of diarrhoea which is clinically distinguishable from acute infective gastro-enteritis.

6. The treatment suggested for acute ileocolitis in children is magnesium sulphate in repeated small doses every morning, together with antidyseutery serum as a routine to combat the toxic symptoms.

## REFERENCES.

1. Andrewes and Inman, *Medical Research Committee, Report No. 42*, Lond., 1919.
2. Baginsky, *Centralbl. f. Bakteriolog.*, 1908, Orig. xlvii. 427.
3. Bahr, *ibid.*, Orig. lxi. 335 and 365.
4. Bloch, *Med. Science Abst. and Rev.*, Oxford, 1921, iv. 12.
5. Board of Health, *Loc. Gov. Bd. Annual Reports Suppl. 1911-12*, xli, App. B, Nos. 3 and 4, 288-329.
6. Braafadt, *Journ. Infect. Dis.*, Chicago, 1923, xxxiii. 434.
7. Charlton and Jehle, *Trans. Assoc. Amer. Phys.*, Philad., 1904, xix. 405.
8. Collins, *Journ. Infect. Dis.*, Chicago, 1905, ii. 625.
9. Duval and Bassett, *Amer. Med.*, Philad., 1902, iv. 417.
10. Findlay, *Brit. Med. Journ.*, 1923, ii. 860.
11. Flexner and Holt, *Rockefeller Institute Monograph on Epidemic Enteritis*, 1904.
12. Graham, *Canadian Med. Assoc. Journ.*, 1921, N. S. xi. 529.
13. Hastings, *Journ. Amer. Med. Assoc.*, 1904, xlii. 1121.
14. Horowitz, *Ann. de l'Inst. Pasteur*, Paris, 1916, xxx. 307.
15. Justi, *Arch. f. Schiffs- u. Tropenhyg.*, Leipz., 1915, xix. 458.
16. Knox, *Journ. Amer. Med. Assoc.*, 1903, xli. 173.
17. Logan, *Lancet*, Lond., 1916, ii. 824.
18. Mackie, *Journ. of Hygiene*, Camb., 1919-20, xviii. 69.
19. Metchnikoff, *Ann. de l'Inst. Pasteur*, Paris, 1914, xxviii. 99.
20. Morgan, *Brit. Med. Journ.*, 1906, i. 908; 1907, ii. 16.
21. Morgan, *Journ. of Hygiene*, Camb., 1911, xi. 1.
22. Nabarro, *Brit. Med. Journ.*, 1923, ii. 857.
23. Park, Collins, and Goodwin, *Proc. N. Y. Path. Soc.*, New York, 1903, iii. 148.
24. Rotch, *N. Y. State Journ. Med.*, New York, iv. 173.
25. Schorer. See Stitt's *Practical Bacteriology*, Philad., 1910, 2nd edit., 177.
26. Schwartz, *Proc. N. Y. Path. Soc.*, New York, 1903, iii. 172.
27. Sonne, *Giftfattige Dysenteribaciller*, Copenhagen, 1914.
28. Teague and Clurman, *Journ. Infect. Dis.*, Chicago, 1916, xviii. 653.
29. Thjøtta, *Journ. Bacteriol.*, Baltimore, 1919, iv. 355.
30. Weaver and Tunnicliffe, *Journ. Infect. Dis.*, Chicago, 1905, ii. 81.
31. Whitehead and Kirkpatrick, *Lancet*, Lond., 1918, ii. 143.
32. Wollstein, *Arch. Pediatr.*, Philad., 1898, lxiv. 760.
33. Wollstein, *Journ. Med. Research*, Boston, 1903, x. 11.



# THE MODE OF INHERITANCE OF HEREDITARY ATAXIA<sup>1</sup>

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## *Introduction: Mendelian Principles involved.*

At the outset of a discussion on the mode of inheritance of hereditary ataxia a brief account of the two Mendelian principles involved may not be out of place. If two individuals differing in respect of one characteristic are crossed the hybrid offspring in the simplest instance all possess a character intermediate between that of the two parents, e. g. red and white flowered varieties of *Mirabilis Jalapa* yielding when crossed a pink flowered hybrid. If now the hybrids are allowed to fertilize themselves, one quarter of the next generation will resemble each of the grandparents and one half will resemble the hybrid. This is explained by the assumption that in the maturation reduction of the chromosomes which occurs during the formation of the germ-cells the hereditary material is halved, each germ-cell receiving, in respect of a given character, an hereditary factor, or 'gene', derived from one or other of the parents, never from both. Thus there are formed germ-cells of two kinds, and if individuals producing these two kinds of germ-cells are crossed the genes become combined in their offspring as follows. If *D* and *R* represent the differing genes

$$DR + DR = DD + DR + DR + RR \text{ or } DD + 2 DR + RR.$$

In the case of many such pairs of characters all the hybrids resemble one parent instead of being intermediate between the two, e. g. if tall and short varieties of pea are crossed all the hybrids are tall. But when interbred they are found to transmit both characters. In such cases the character which is exhibited by the hybrids of the first generation is called dominant and the latent character recessive. If in the above equation *D* signifies a dominant and *R* a recessive character, it will be seen that three-fourths of the second filial generation will show only the dominant character, but of these only one-third, *DD*, will be pure or 'homozygous' dominant and capable of transmitting only the dominant character: two-thirds will be hybrid, or 'heterozygous', *DR*, and capable of transmitting both dominant and recessive characters.

When two pairs of such Mendelian characters are under consideration, it is found that each pair behaves independently of the other in the maturation

<sup>1</sup> Received April 28, 1925.

divisions, and there are thus four different sorts of germ-cell possible. If  $A$  and  $a$ ,  $B$  and  $b$  represent the two pairs of characters, these will be  $AB$ ,  $Ab$ ,  $aB$ ,  $ab$ , and the possible modes of combination will be correspondingly increased.

*The Inadequacy of Current Theories to explain the Inheritance of Hereditary Ataxia.*

Hereditary ataxia is a disease which is exhibited and transmitted by both sexes. Its mode of inheritance has been discussed by a number of authors; the hereditary factor being believed by some to behave in inheritance as a dominant and by others as a recessive character. Only three authorities, Dresel (5), Bergman (1), and Mino (9), have brought forward evidence in support of their conclusions. Dresel, on statistical evidence alone, distinguishes an 'atypical' form of hereditary ataxia which behaves as a dominant and a 'typical' form (Friedreich's) which behaves as a recessive. Bergman, from a consideration of the mode of inheritance in four families, reaches the conclusion that in the case of Marie's cerebellar ataxia 'the numerical proportion between the healthy and sick persons agrees remarkably well with the assumption of a recessive inheritance', but 'the appearance of the disease in other respects agrees better with the assumption that the inheritance is of a dominant nature'. In Friedreich's ataxia he considers recessive inheritance the more probable. Mino alone examines the mode of inheritance both in a particular family and by statistical methods. His very thorough survey of the literature has enabled him to collect 268 cases. He concludes that hereditary ataxia is inherited as a recessive, although, as he admits, there is a serious unexplained discrepancy between the proportion of affected to normal offspring expected on this hypothesis and that actually obtained.

It is thus clear that there is no agreement among different authors as to whether hereditary ataxia is a dominant or recessive character, and the three authorities who have devoted most attention to the subject all find it difficult to assign the disease satisfactorily to either of these categories. The possibility must be considered that it is a character which sometimes behaves as a dominant and at other times as a recessive. Such an alternation depending on environmental changes is known to occur in insects (10), but in man its occurrence could hardly be proved. There is, however, as will be seen later, evidence that the mode of inheritance in hereditary ataxia is constant and not variable.

In view of Dresel's opinion that a different mode of inheritance obtains in cerebellar ataxia and in Friedreich's disease it is necessary to justify the method adopted by Mino and in this paper of treating the different forms of hereditary ataxia as a single homogeneous group. It has long been evident that neither clinically nor pathologically can a clear-cut distinction be drawn between forms of the disease affecting the spinal cord only and those in which the cerebellum alone is involved, since numerous intermediate forms have been described. The view advocated especially by Jendrassik (8) and Raymond (11) and more recently by Schaffer (13, 14) is now generally accepted, viz. that in all these forms of the

disease the essential underlying process is the same and that they differ only in respect of its distribution in the nervous system and its intensity.

Dresel's conclusions are based on statistical considerations alone, and these, if unsupported by an examination of the mode of inheritance in particular families, are inadequate and may be misleading. In investigating the inheritance of a disease in man both sources of data must be utilized. The number of cases in particular families is too small to afford positive evidence, but particular instances often render it possible to exclude modes of inheritance which are incompatible with them. On the other hand, statistical results alone may be compatible with several explanations, of which the true one can only be arrived at by a consideration of particular instances. Moreover such instances alone can furnish the data which are required to decide the nature of the corrections which must be applied to the statistics. For this reason Dresel's figures must be discarded. An examination of families in which hereditary ataxia has appeared in more than one generation, whether the disease has been of the cerebellar or spinocerebellar form, as in the cases reported by Sanger Brown (3), Bergman (1), and Sprawson (15), or of Friedreich's form as in the cases of Bergman (1), Biro (2), Carré (4), Rüttimeyer (12), and Vizioli (16), does not support Dresel's view that in respect of the mode of inheritance a distinction can be drawn between them.

It is proposed in this paper to show that the inheritance of hereditary ataxia cannot be explained on the assumption that it behaves as a single Mendelian factor, either dominant or recessive; but that it is more complex and depends on the presence of two Mendelian factors, one of which is a dominant and the other a recessive.

In order to show the inadequacy of a single Mendelian factor to explain the facts of the inheritance of the disease, no better example can be chosen than the family reported by Sanger Brown (3), and discussed in this connexion by Mino (Fig. 1). In this family the disease was transmitted from the first case through three apparently normal persons, II 5, III 5, and IV 5, and affected two members of the fifth generation, V 1 and 2. The hereditary factor must therefore have been present in a latent form in the three intermediate descendants of the original case. This latency cannot occur in the case of single Mendelian dominants, since all bearers of the character, whether pure  $DD$  or heterozygous  $DR$ , exhibit it, while pure recessives,  $RR$ , cannot transmit it. On the other hand, the implications of the view that the disease behaves as a single Mendelian recessive seem to have been inadequately appreciated by its advocates and to render it equally impossible of acceptance. In order that a recessive character may appear in the offspring of a given mating, the character must have been present in both parents, since if one parent is without it,  $DD$ , all the offspring will contain the dominant factor and fail to show the recessive. It will be noted that in the family described by Sanger Brown ten out of twelve marriages resulted in affected offspring. Neither the presence nor the absence of consanguinity is mentioned by Sanger Brown. If it had occurred it would almost certainly have been noted, and in any case it is most unlikely to have occurred frequently. Hence, if the disease

is to be considered a Mendelian recessive, it is necessary to suppose that ten out of twelve members of the population were heterozygous for the recessive factor ( $DR$ ). Mino is therefore compelled to assume that the recessive factor was very common in the neighbourhood. But if this were so 25 per cent. of the offspring of about three-fourths of the marriages of the general population would be affected ( $DR + DR = DD + 2 DR + RR$ ).

Actually the condition is extremely rare; and it therefore seems impossible that it can be a Mendelian recessive.

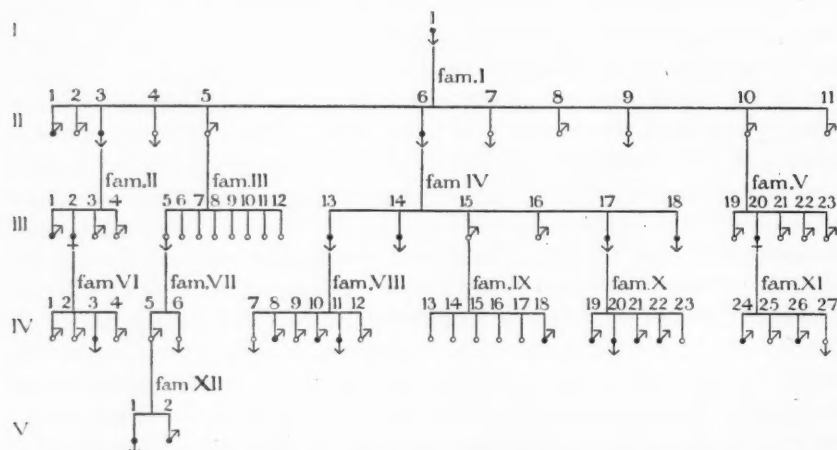


FIG. 1. Pedigree of family reported by Sanger Brown: black circles indicate ataxic members.

*Evidence in Favour of the Hypothesis proposed.*

It remains to show that the mode of inheritance can be explained on the assumption that two Mendelian factors must be present, one a dominant arising as a mutation in a progenitor of the affected persons, the other a recessive character more or less diffused throughout the general population. It is the assumption of two factors which renders it possible to avoid the difficulties which are encountered by theories which assume the presence of one only. For this purpose the second factor might be either a dominant or a recessive, but, as will be seen later, the statistical evidence is in favour of the latter.

It is proposed to indicate the mutant factor arising in the affected family by the letter  $M$  and the accessory factor by the letter  $a$ , dominance being indicated by the use of a capital letter and recessivity by a small letter. Affected persons may therefore be either pure dominant or heterozygous for the mutant factor  $M$ , but they must be pure recessive for the accessory factor  $a$ . Two types of affected persons may therefore occur,  $MMaa$  and  $Mmaa$ . The former can only arise from the mating of two stocks already possessing the mutant factor, and this, in the absence of consanguinity, must be extremely rare.  $Mmaa$  therefore alone need be considered. Normal persons, i.e. those not possessing the dominant mutant factor, may be of three types,  $mmaa$ ,  $mmAa$ , and  $mmAA$ , i.e. they are all pure

# THE MODE OF INHERITANCE OF HEREDITARY ATAXIA 355

recessive for the mutant factor, but may be pure recessive, heterozygous, or pure dominant for the accessory factor. There are therefore three possible matings for an affected person with the following results:

$$\begin{array}{l}
 (1) \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & a \\ \hline m & a \\ \hline \end{array} = 2 \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \end{array} + 2 \begin{array}{|c|c|} \hline m & a \\ \hline m & a \\ \hline \end{array} \\
 \text{Affected} \quad \text{normal} \quad \text{Affected} \quad \text{normal} \\
 \\
 (2) \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & A \\ \hline m & a \\ \hline \end{array} = \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \end{array} + \begin{array}{|c|c|} \hline M & A \\ \hline m & a \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & A \\ \hline m & a \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & a \\ \hline m & a \\ \hline \end{array} \\
 \text{Affected} \quad \text{normal} \quad \text{Affected} \quad \text{healthy (latent)} \quad \text{normal} \quad \text{normal} \\
 \\
 (3) \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & A \\ \hline m & A \\ \hline \end{array} = 2 \begin{array}{|c|c|} \hline M & A \\ \hline m & a \\ \hline \end{array} + 2 \begin{array}{|c|c|} \hline m & A \\ \hline m & a \\ \hline \end{array} \\
 \text{Affected} \quad \text{normal} \quad \text{Healthy (latent)} \quad \text{normal}
 \end{array}$$

Percentage  
affect Lat N

50 0 50

25 25 50

0 50 50

FIG. 2.

It will be seen that certain of the offspring of a marriage between an affected and a normal person, represented by the formula  $MmAa$ , do not exhibit the disease since they are heterozygous for the recessive factor, but since they possess the dominant mutant factor they are capable of transmitting it. As long as this 'latent' type mates only with the  $mmAA$  type of normal none of the offspring will exhibit the disease since none will be pure recessive for the accessory factor. Half of the offspring of such a mating will be normal; one quarter will reproduce the parental 'latent' type  $MmAa$ , while the other quarter will be of the alternative 'latent' type,  $MmAa$ , i.e. pure dominant for the accessory factor. Both of these 'latent' types can transmit the disease, but the second is interesting in that the disease cannot reappear earlier than in the second generation of its descendants, since none of the first generation will be pure recessive for the accessory factor. In either case the disease reappears after latency as a result of the mating of the first latent type  $MmAa$  with a type of normal either heterozygous or pure recessive for the accessory factor. A proportion of the offspring of either of these unions will exhibit the disease.

It is thus clear that the mode of inheritance proposed permits of the transmission of the disease by members of the family in whom it is latent and yet accounts for its occurrence in the families resulting from the union of affected and healthy persons without its being prevalent in the general population. It remains to ascertain how far it is supported by the available statistical evidence. To do this it is necessary to consider what proportion of the offspring is likely to exhibit the disease if this mode of inheritance actually occurs and to compare the expected percentage with that actually found. It is necessary to consider separately the offspring resulting from the union of an affected and a normal

marriage of comm latent  $Mm Aa$  with three types of normal

	all	Pat	Normal
(1)	25	25	50
(2)	12.5	37.5	50
(3)	0	50	50

Patent 2 Pa 1  
all  $Mm Aa$   $Mm Aa$   
 $\frac{2}{3}$   $Mm Aa$   
 $\frac{1}{3}$   $Mm Aa$



person and those resulting from the union of two apparently healthy persons, since the expected proportion of affected offspring differs in the two cases.

Mino has therefore divided his 268 cases into these two groups. In each group he has calculated the proportion of affected offspring, and finds it, when corrected by Weinberg's methods for statistical errors, to be 30 per cent. in the former and 13.4 per cent. in the latter.

To consider the former group first, it has been suggested above that there are available as mates for an affected person three types of normal differing only in being pure recessive, heterozygous, and pure dominant for the accessory factor. The last mating, (3) above, does not result in affected offspring in the first generation. Since all Mino's families contain affected offspring they must therefore have been derived from one or other of the two remaining matings. Of these (1) is expected to yield 50 per cent. of affected offspring and (2) 25 per cent. The proportion of affected persons in the mixed offspring resulting from a large number of matings of both types is an average and will be between 50 per cent. and 25 per cent., the exact figure depending on the relative number of the two types of normals in the population. Thus if pure recessives for the accessory factor were largely in excess of heterozygotes, the figure would approach 50 per cent.; if the latter were much the commoner, it would approach 25 per cent. Unfortunately there are no data available from which the relative proportions of these types of normal can be calculated, and it has been shown by Hardy (7) that Mendelian dominants, heterozygotes, and recessives may exist in stable equilibrium in a mixed population indefinitely, their relative proportions depending simply on the relative numbers of dominants and recessives, which may exist in any conceivable ratio. All that can be said on this point therefore is that on the hypothesis proposed the average proportion of affected offspring resulting from a large number of matings of affected and normal persons is expected to be between 50 per cent. and 25 per cent., and was in fact found by Mino to be 30 per cent. By a similar calculation it can be shown that the proportion of affected offspring resulting from the mating of two apparently normal persons should be between 25 per cent. and 12.5 per cent., and was found by Mino to be 13.4 per cent. Mino's figures then are quite consistent with the hypothesis proposed in this paper, that the inheritance of hereditary ataxia depends on the presence of two Mendelian factors, one of which is a dominant and the other a recessive; but they can hardly be reconciled with his own assumption that the disease is inherited as a simple Mendelian recessive character, which would yield 50 per cent. of affected offspring in the first group

$$(DR + RR = 2 DR + 2RR)$$

and 25 per cent. in the second

$$(DR + DR = DD + 2 DR + RR).$$

This discrepancy Mino himself notes, but fails to explain.

It was said above that the assumption of two factors, both of which were dominant, would account equally well for the mode of inheritance in particular

\* If there are chance distributions 33 1/3% would be expected instead of 30% found which is good agreement. (16.75%)



instances, but it can be shown that such a basis for inheritance would yield an expected proportion of affected offspring much too high. Thus if both factors were dominant the offspring of the mating of two apparently normal persons would be represented as follows:

$$\begin{array}{lcl}
 \text{(1)} & \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \text{Healthy} & \\ \text{(latent)} & \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & A \\ \hline m & A \\ \hline \text{normal} & \\ \hline \end{array} & = & 2 \begin{array}{|c|c|} \hline M & a \\ \hline m & A \\ \hline \text{Affected} & \\ \hline \end{array} + 2 \begin{array}{|c|c|} \hline m & a \\ \hline m & A \\ \hline \text{normal} & \\ \hline \end{array} \\
 \\
 \text{(2)} & \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \text{Healthy} & \\ \text{(latent)} & \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & A \\ \hline m & a \\ \hline \text{normal} & \\ \hline \end{array} & = & \begin{array}{|c|c|} \hline M & a \\ \hline m & A \\ \hline \text{Affected} & \\ \hline \end{array} + \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \text{healthy} & \\ \text{(latent)} & \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & a \\ \hline m & A \\ \hline \text{normal} & \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & a \\ \hline m & a \\ \hline \text{normal} & \\ \hline \end{array} \\
 \\
 \text{(3)} & \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \text{Healthy} & \\ \text{(latent)} & \\ \hline \end{array} + \begin{array}{|c|c|} \hline m & a \\ \hline m & a \\ \hline \text{normal} & \\ \hline \end{array} & = & 2 \begin{array}{|c|c|} \hline M & a \\ \hline m & a \\ \hline \text{Healthy} & \\ \text{(latent)} & \\ \hline \end{array} + 2 \begin{array}{|c|c|} \hline m & a \\ \hline m & a \\ \hline \text{normal} & \\ \hline \end{array}
 \end{array}$$

FIG. 3.

Here mutant and accessory factors are both dominant, and it will be seen that only matings (1) and (2) yield affected offspring; the former in the proportion of 50 per cent. and the latter of 25 per cent. If both hereditary factors are dominant, then, the proportion of affected offspring resulting from the mating of two apparently normal persons should lie between 50 per cent. and 25 per cent., whereas it was found by Mino to be 13.4 per cent. in this group.

There is a further point in support both of the view that a recessive factor is involved and that Mendelian principles are applicable to this disease. Mino found the proportion of affected offspring in the two groups to be 30 per cent. and 13.4 per cent., and these figures are in a ratio of 2.2:1. This ratio, which approximates to 2:1, can readily be understood if a Mendelian recessive factor is present. In the group yielding the higher proportion one parent is affected; in the other group both parents are apparently normal. Mendelian principles assume that in order that a recessive character may be exhibited a double dose must be present: if a single dose only is present the character remains latent but can be transmitted. On this assumption it is readily intelligible that an affected parent should produce twice as many affected offspring as a parent in whom the disease is latent. It is difficult to explain this ratio by means of any hypothesis which does not involve unit factors. Further, it is only the recessive factor which yields this 2:1 ratio, and it can be shown that if both factors were dominant the ratio would be much lower.

The third possible combination of two Mendelian factors is that they should both be recessive; but this is open to the same objections which render inappli-

cable the hypothesis of a single recessive factor and which have already been considered.

The mode of inheritance in which the exhibition of a disease depends on the presence of two Mendelian factors which become independently assorted in the maturation reduction divisions is considered by Dresel (5) as a possible explanation of the transmission of a disease through apparently normal persons in cases where there is reason to doubt its recessive character. Hall (6) has also suggested it in order to account for the mode of inheritance of progressive lenticular degeneration in a family which he reports and in which a similar latency occurred.

#### Summary.

1. The mode of inheritance of hereditary ataxia cannot be explained on the assumption that the disease behaves as a single Mendelian character, whether dominant or recessive.

2. It can be satisfactorily explained if it be assumed that the disease depends on the presence of two Mendelian characters, one of which is a dominant and the other a recessive.

3. The percentage of affected offspring expected on this hypothesis is consistent with that actually found.

*an excellent paper*

#### REFERENCES.

1. Bergman, E., *Upsala Läk. Förhandl.*, Hörh, 1921, xxvi. iv. 1.
2. Biro, *Deutsch. Zeitsch. für Nervenheilk.*, Leipzig, 1901, xix. 164.
3. Brown, S., *Brain*, Lond., 1892, xv. 250.
4. Carré, quoted by Friedreich, *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1876, lxviii. 145.
5. Dresel, *ibid.*, 1917, ccxxiv. 256.
6. Hall, H. C., *La dégénérescence hépato-lenticulaire*, Paris, Masson, 1921; abst. *Brain*, Lond., 1921, xlv. 588.
7. Hardy, G. H., *Science*, New York, 1908, N. S., xxviii. 49.
8. Jendrassik, R., *Lewandowsky's Handbuch der Neurologie*, 1911, ii. 321.
9. Mino, P., *Il Policlinico, Sez. Med.*, Roma, 1922, xxix. 615.
10. Morgan, T. H., *Physical Basis of Heredity*, Philad. and Lond., 1919, 28.
11. Raymond, F., *Pathologie nerveuse*, Paris, 1910.
12. Rüttimeyer, *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1893, xci. 106.
13. Schaffer, K., *Schweiz. Archiv f. Neur. u. Psych.*, Zürich, 1920, vii. 193.
14. Schaffer, K., *Deutsch. Zeitschr. f. Nervenheilk.*, Leipzig, 1922, lxxiii. 101.
15. Sprawson, C. A., *Brit. Med. Journ.*, 1914, i. 23.
16. Vizioli, abs. *Neurol. Centralblatt*, Leipzig, 1886, v. 111.

## HEREDITY IN POLYCYSTIC DISEASE OF THE KIDNEYS<sup>1</sup>

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With Plate 17

### *Introduction.*

WITH few exceptions the diseases so far shown to be hereditary present but little difficulty in diagnosis. In hereditary affections such as haemophilia, diabetes insipidus, mental deficiency, the hereditary deformities of the limbs, lip, and palate—in all of these there is present some striking and diagnostic sign which can be, and usually is, accurately recorded by the lay observer. The recurrence of such a taint within its ranks becomes an integral part of the family's tradition, and the discovery that the disease is hereditary comes usually from within the family itself.

Polycystic disease of the kidneys is an affection in which demonstration of any existing hereditary influence might well be difficult, as consideration of the clinical manifestations of the disease will show. It may occur as a congenital condition, when the large kidneys of the foetus commonly cause obstruction to labour. In the 'adult' type of the disease the early symptoms may be those of slight uraemia, or may be entirely urinary (haematuria, renal colic, disturbances of micturition), or may merely consist of long-continued and troublesome dyspepsia; while death may be due to uraemia, sometimes of sudden onset, or to cerebral haemorrhage, or may result, even in the aged, from some quite independent affection, the cystic kidneys being discovered only at necropsy.

It is not surprising, therefore, that diagnosis of this disease often presents great difficulty, and that, in a disease taking such varied forms, an hereditary origin might readily escape notice.

By a fortunate series of events I have been able to secure evidence of the occurrence of polycystic disease of the kidneys in three successive generations of a family residing in the East End of London. The disease occurs with such frequency in the second and third generations as to leave little doubt of its hereditary origin.

Evidence for the hereditary nature of polycystic disease of the kidneys has

<sup>1</sup> Received June 19, 1925.

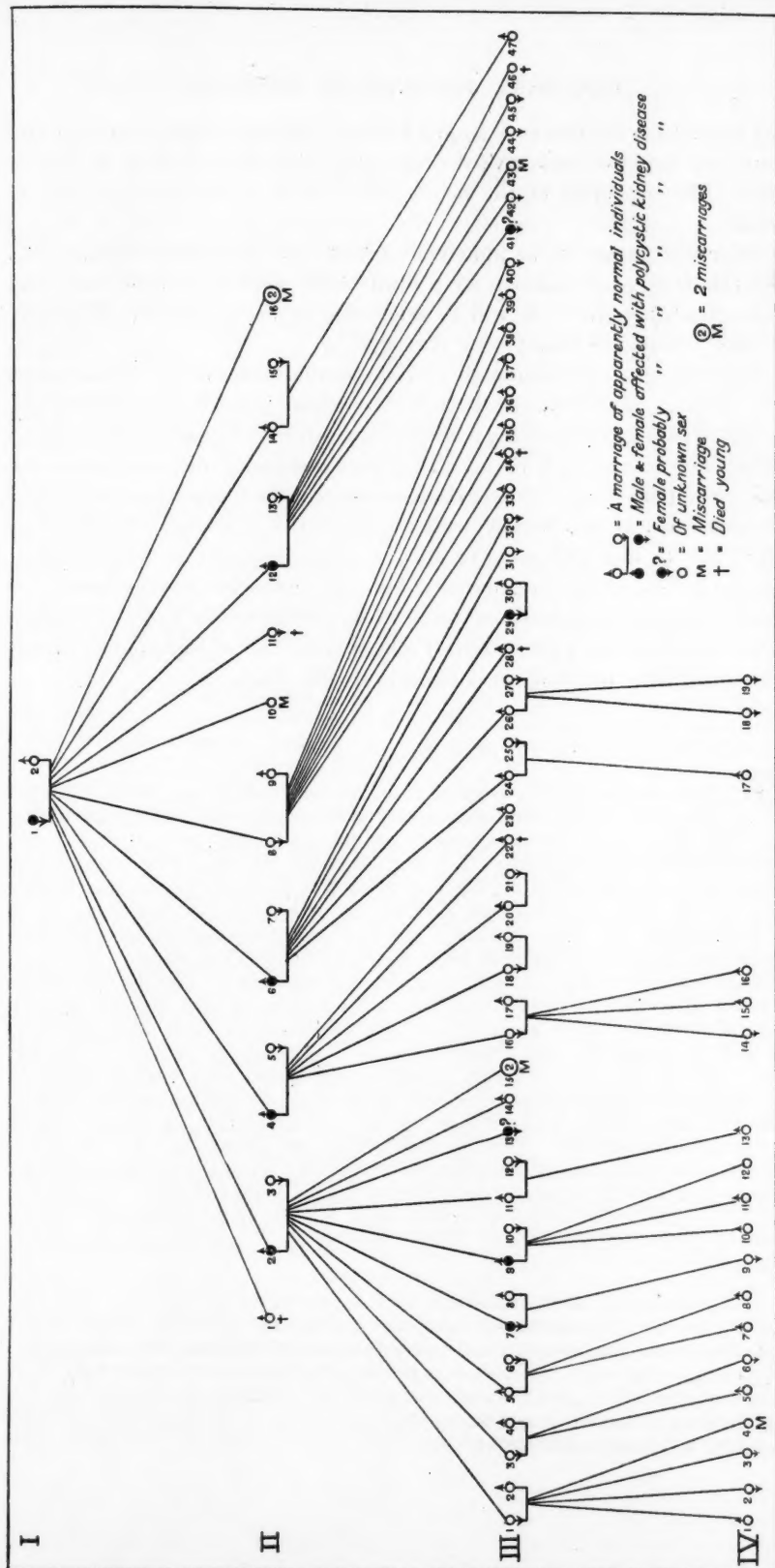
already been brought forward by a number of writers, notably Bull (6) and Dunger (11), yet to judge from the literature on the disease there is no general recognition of this fact.

I propose in this paper to record the medical history of the family which I have studied; then to examine evidence collected from the literature; and, finally, to collect and group the facts about heredity in polycystic disease of the kidneys.

#### PART I. *The East London Family.*

The investigation was carried out at the London Hospital, which, it appears, has long been the chief refuge of this family in times of sickness. The first case studied was that of a young married woman who came as an out-patient to Dr. Theodore Thompson's clinic. She complained of haematuria and was obviously suffering from polycystic kidney disease. She stated that her father and several of his brothers had had haematuria and had ultimately died of some kidney disease. Dr. Thompson, who already knew and had written (25) on the hereditary nature of polycystic kidney disease, very kindly allowed me to study his case, and thus the family history. From the London Hospital records I learnt that not only the father and uncles of Dr. Thompson's patient, but also the grandmother had had polycystic kidney disease. Gaps in the information concerning various members of the family were filled from the records of other hospitals kindly placed at my disposal; information thus obtained is acknowledged in the case reports. Subsequently, through the kindness of my chief, Mr. Hugh Lett, I was able to examine, in his wards and in the Genito-urinary Department, several living members of the family; one of these was sent, quite independently, by his doctor to Mr. Lett, at a time when I was despairing of tracing his branch of the family, and he, too, proved to have polycystic kidneys.

The pedigree of the family is displayed in Fig. 1, and is described in the following pages. In the description the roman numerals refer to the generation, the arabic to the member of that generation. The year of birth, when known, is placed in brackets after the pedigree number and name of the individual. I. 1, Susannah H. (1842), is the first member of the family in whom I can find any evidence of polycystic kidney disease. I have limited the present description to her and her direct descendants because investigation of the collateral members of the family is not yet complete. I hope to make a full report upon these at a later time, and only a few facts outside the pedigree, as it is here presented, need now be noted. I. 1 was the youngest of a family of eight. Her father and mother were born in London in the first decade of the nineteenth century, and engaged with their children in the silk-weaving trade. So far I have found no indications of the existence of polycystic disease of the kidneys in collateral members of the family, but it is impossible to conclude that I. 1 is a *de novo* case; for it is recorded that the father of I. 1 died at the age of 41 of 'liver disease', a diagnosis which might well have been given eighty years ago to a case of polycystic disease of the kidneys and liver. Some of the nieces and nephews



**FIG. 1. East London family (no consanguinity).**

of I. 1 migrated to the United States of America (? Chicago) many years ago, and some of her grandchildren have recently gone with their children to live in Canada. The remainder of the family still live in or near the East End of London.

Polycystic disease of the kidneys is not the only hereditary affection from which this family has suffered, for a considerable number of them have had myopia of high degree. It will be interesting to inquire whether these two hereditary defects are in any way connected.

It is necessary to note in passing certain peculiarities of temper which existed in the family. While some of them were tractable, pleasant folk, the majority appeared extremely self-sufficing: indeed, they carried independence to a degree at which it ceases to be a virtue. They were essentially 'difficult' people and needed careful handling. Most of them readily submitted themselves for medical examination, but it was usually with the stipulation that they should not be brought face to face with some or other of their relatives; so many of them seemed to be 'not on speaking terms'. I am at a loss to find a better description for these temperamental deficiencies, and am at present unable to decide whether they are hereditary in origin or merely geographical; for of East End families it has been said that 'they only meet for funerals and marriages'.

#### *First Generation.*

I. 1, Susannah H. (1842), married I. 2 when 23 years of age, and during the next 17 years had by him 8 children and 3 miscarriages. A younger step-sister, who is still alive, states that even as a young woman I. 1 had no sight in one eye, but that she never wore glasses. I. 1 had polycystic disease. Her illness began in 1878, when, at the age of 36, she had what was probably haematuria lasting 24 hours. In 1882, after her last confinement, she noticed a swelling on each side of the abdomen. Two years later she had haematuria continuously for three months, and in addition suffered from anorexia, flatulence, abdominal pain, and occasional attacks of misty vision, dizziness, and vomiting. During this illness she was in the London Hospital and was found to have a hard nodular mass in the right side of the upper abdomen. The urine contained much blood and albumen and an occasional cast; specific gravity, 1014; daily output, 60 to 100 ounces. There was slight outward displacement of the apex beat of the heart. The symptoms disappeared under medical treatment. In 1888 she was readmitted to the London Hospital, under the care of the late Dr. Sutton, in a state of great exhaustion and dyspnoea. Oedema of the lungs was observed. The urine was clear and free from albumen; specific gravity, 1020. The patient rapidly became comatose and died thirty-six hours after admission. Post-mortem examination was made; the detailed notes cannot be found, but the summary states: 'Cystic disease of the liver and kidneys. Left kidney on sacrum in true and false pelvic cavities.'

I. 2, Charles L. (1841), husband of I. 1, served behind the bar and was, according to his descendants, his own best customer. After the death of I. 1 he married his first wife's niece and had by her several children, for whom search is at present being made. I. 2 died in the Mile End Hospital in 1898, being then 57 years of age. Dr. J. I. P. Wilson has kindly informed me that death was due to 'pulmonary tuberculosis and haemoptysis'. I have learnt from the step-sister of I. 1 that I. 2 had good eyesight.



*Second Generation.*

*II. 1*, Charles L. (c. 1866), the eldest child of *I. 1* and *I. 2*, died in his second or third year from an unknown cause.

*II. 2*, George L. (1870), died in Poplar Hospital from polycystic disease of the kidneys and liver at the age of 46. I have been unable to obtain detailed notes of this case owing to the destruction by flood of a number of the Poplar Hospital records. But, with the kind assistance of Dr. Paul Watkin, who attended *II. 2* and his family, I have been able to obtain a considerable amount of information about the patient. *II. 2* was extremely short-sighted. His health was good until eight months before his death, when he became very languid and suffered from severe pains in the back. He gradually got worse, and two months before his death he had to give up work and take to his bed. In the last fortnight of his life he had slight haematuria and some epistaxis. He was admitted to the Poplar Hospital on May 14, 1916, and died three days later, having been unconscious for one or two hours before death. Post-mortem examination was carried out, and afterwards death was certified as being due to 'Congenital cystic kidneys and liver. Uraemia.' The relatives were told at the hospital that the symptoms from which *II. 2* suffered had been due to the gradual destruction of the kidney substance by cysts. It appears, therefore, that *II. 2* undoubtedly had polycystic disease.

*II. 3*, Ann G. (1868), became the wife of *II. 2* and eight children resulted from the union. *II. 3* suffered from renal calculus. In 1912 stones were removed from the right kidney. Fourteen months later the wound, which had never healed, discharged some gauze packing. In 1916 the patient developed a perinephric abscess for which she was treated in the London Hospital. She died in 1919 of perinephric abscess and lardaceous disease.

*II. 4*, Alfred L. (1872), third son of *I. 2*, also had polycystic disease of the kidneys. From 1899 onwards he had occasional slight pains in the back, but these did not become severe until 1913, when, at the age of 41, he began to have a constant aching pain in the right lumbar region, made worse by exertion. In April 1919 he had severe haematuria, followed three days later by typical right-sided renal colic and vomiting. He was admitted to the London Hospital, under the care of Mr. Furnival. The abdomen was generally tender and deep palpation was impossible owing to the associated rigidity; but later, under an anaesthetic, both kidneys were found to be enlarged and nodular and the liver also was enlarged. Radiographic examination of the urinary tract showed enlargement of the right kidney, and, in the left kidney region, a small shadow of uncertain nature. The urine was acid and contained a cloud of albumin and a deposit of blood; specific gravity, 1009. The bladder was normal at cystoscopy. The left ureter was catheterized, and from it came urine containing 0.6 per cent. of urea, a heavy cloud of albumin, and a deposit of blood and epithelial cells. A catheter twice passed up the right ureter met with obstruction 5 cm. above the ureteric orifice; its withdrawal was followed by a gush of thick coffee-coloured material. The colic and haematuria subsided with rest. A diagnosis of polycystic kidney disease was made and medical treatment advised. Of the subsequent history only the final illness is known. In August 1923, *II. 4* was admitted during an attack of haematuria to Whipps Cross Hospital (Medical Superintendent, Dr. J. C. Muir). A double pyelogram, done by Mr. Clifford Morson, showed that the renal pelves, though incompletely filled by the opaque solution, were obviously enlarged, and on one side the calyces were broader than normal. Operation was not advised, so the patient took his discharge. He died at home on September 8, 1923, being then 51 years of age. There can be little doubt that this was a case

of polycystic disease of the kidneys. It is possible that the liver enlargement was due to cysts. II. 4 was short-sighted. In 1919 the report from the Ophthalmic Department of the London Hospital was: 'Nebulae over both corneae. Right pupil fixed and contracted. Degenerative changes in left lens. Some vitreous opacities. The condition is one of high myopia.'

II. 5, Eleanor N. (1877), became the wife of II. 4 and had by him five children. When last seen, in March 1925, she was in good health.

II. 6, Ernest L. (1874), fourth son of I. 1 and I. 2, began to show symptoms of polycystic disease of the kidneys at the age of 36, when, on March 31, 1910, he had haematuria, which was followed by pain in the right loin, vomiting, and severe headache. Micturition was not frequent. He was admitted during the attack to the London Hospital. The urine contained blood and a corresponding amount of albumin. There was great rigidity of the abdominal wall on the right side. X-ray examination, on two occasions, showed a shadow, the size of a bean, in the right kidney region, and a diagnosis of right renal calculus was made. Mr. Openshaw explored the right kidney. It was a typical polycystic kidney, studded with cysts up to the size of a walnut. The kidney was not removed. After the operation the patient continued to have attacks of haematuria until his death in 1922. He would have 'bad days': in the morning he would suffer from languor, severe frontal headache, and 'a terrible feeling of dry burning heat all over the body'; then the haematuria would begin, to be followed or not by pain in the left loin. After each attack he would feel well and full of energy, and would remain thus for as long as a month. In the last year of his life he suffered from intolerable itching of the skin and had several fits, which lasted only a few minutes, and were followed by complete recovery. He died at home in November 1922. All his life II. 6 suffered from defective vision. In 1910 Mr. Roxburgh reported on his eyes as follows: 'Vision 3/60 in right eye and "fingers at a foot" in the left. Double choroido-retinitis, and in each eye evidence of old iritis without any vitreous opacities. The defect in the right eye appears to be due to choroidal atrophy affecting chiefly the macula, whereas in the left eye the defect appears to be the result of the old iritis. The eye changes, considered as a whole, distinctly suggest congenital syphilis.' I can find no trace of syphilis in any other member of this family, and the patient himself had a negative Wassermann reaction in 1921. It is possible, therefore, that the eye changes were not produced by congenital syphilis; the defect of sight may have been rather due to myopia.

II. 7, Alice A. (1877), was the wife of II. 6, and had by him six children. When last seen, in April 1925, she was in good health.

II. 8, Emily L. (1875), is now the only surviving child of I. 1 and I. 2. She is married and has eight children. Examined recently she showed, at the age of 50, no signs of polycystic disease. She was complaining of abdominal pain and flatulence after meals, which eased when she lay down; but she was otherwise perfectly well. She had never had any trouble with her water. Her abdominal wall was very weak. The right kidney was palpable but not enlarged, the left kidney could not be felt. An inguinal hernia was present on both sides. No specimen of urine could be obtained. Her eyesight was good and she had never worn glasses. The abdominal symptoms from which she suffered were almost certainly due to 'visceroptosis'.

II. 9, William D. (1875), husband of II. 8, was reported to be alive and well in March 1925.

II. 10, a miscarriage. According to her own statement, made in the London Hospital in 1884, I. 1 had the last of her three miscarriages in 1876.

II. 11, Rosa L., younger sister of II. 8, died when about two years old. II. 8 has been told that II. 11 died as the result of a fall from a bassinet on to her head. The date of birth of II. 11 is not known, but from the information of several survivors it appears that her position in the pedigree is here correctly recorded.

II. 12, Albert L. (1880), the next child of I. 1 and I. 2, as a young man developed chronic bronchitis and had lung trouble for the rest of his life. Symptoms of polycystic disease of the kidneys first appeared in February 1911, when, at the age of 31, he had painless haematuria for a week. Shortly after this attack he was admitted to the London Hospital, under the care of Mr. Dean. The right kidney was found to be greatly enlarged, its outline was irregular, and on its surface nodular excrescences could be felt. The urine was clear and free from albumin; specific gravity, 1018; urea, 1 per cent.; no microscopic deposit. The bladder was normal at cystoscopy. Medical treatment was advised. A few months later II. 12 began to have pain in the right loin, and in May 1912 the pain became so severe that he was admitted to King's College Hospital. Sir Watson Cheyne explored the right kidney and found that it was composed of multiple cysts. He decided not to remove the kidney, and before closing the abdomen, he opened the peritoneal cavity and ascertained that the left kidney also was cystic. In July 1918 II. 12 was again in King's College Hospital, under Dr. Raymond Crawford, on account of abdominal pain, vomiting, and haematuria. In the following winter his lung trouble became very bad, and he died in Dr. Crawford's wards in February 1919. At necropsy an abscess was found in the lower lobe of the right lung, and both lungs showed oedema and severe purulent bronchitis. The kidneys consisted almost entirely of cysts, and of the normal kidney tissue little remained. The kidneys together weighed 3 lb. 4 oz., the left kidney being slightly the heavier. The liver was enlarged and contained 'what appeared to be a small cyst'. I am informed that II. 12 had good sight.

II. 13, Mary M. (1882), was the wife of II. 12 and bore him five children, the last of whom was still-born; in addition she had one miscarriage. In August 1916 she was admitted in labour to St. Andrew's Hospital; the medical superintendent, Dr. Le Clezio, has kindly informed me that the labour was complicated by placenta praevia, and that the patient died shortly afterwards of septicaemia.

II. 14, Bert L. (1882), youngest son of I. 1 and I. 2. Several of the surviving members of the family are under the impression that II. 14 had polycystic disease of the kidneys, but when cross-examined they have been able to produce no evidence in support of this statement. Dr. C. Thackray, medical superintendent of St. Pancras Hospital, has kindly informed me that II. 14 died of lobar pneumonia on June 9, 1914. It is said that he had good sight.

II. 15, wife of II. 14, had one child and died *circa* 1922. Nothing else is known about this woman.

II. 16, two miscarriages of I. 1. The dates of these miscarriages are unknown, but they must have occurred early in the married life of I. 1 and I. 2, for, according to the statement of I. 1 herself, the last miscarriage, II. 10, occurred in 1876. It is probable that the two miscarriages occurred before the birth of II. 6.

### *Third Generation.*

I. 1 had 33 grandchildren. Four of these died in infancy, and one other was killed in the Great War. Of the remaining 28 I personally examined 20 and saw four others who would not submit themselves to medical examination. Two others were residing in Canada; another, being pregnant, could not attend for

examination, and one I was unable to trace. Of the 20 examined by me three had polycystic disease and two others were probably similarly affected. In this and the following generation the observations recorded were made by me during March and April 1925, unless otherwise stated.

*III. 1*, Alice L. (1888), eldest child of *II. 2* and *II. 3*, complained of slight pain in the right iliac fossa. She had 'visceroptosis' and a right femoral hernia—quite enough to account for her symptoms. Both kidneys could be felt; they were not enlarged and their surfaces were smooth. Urine: acid, clear, no albumin; specific gravity, 1012. *III. 2*, Conrad G. (1887), husband of *III. 1*, was said to be well. *III. 3*, Annie L. (1890), living in Ontario; said to be short-sighted and to wear glasses. *III. 4*, Henry R., husband of *III. 3*, no information. *III. 5*, George L. (1892), suffered from dyspepsia for a short time during 1924, but otherwise had enjoyed good health. Right kidney palpable, not enlarged. Urine: no albumin; specific gravity, 1012. His wife, *III. 6*, Hannah O. (1894), said to be well.

*III. 7*, Emily Daisy L. (1897), was quite well until September 1922, when she had an attack of haematuria, with pain in the right loin and great frequency of micturition. The haematuria preceded the pain. She was examined by X-rays but no stone was found. By the end of a week her symptoms had practically disappeared, and she had had no further trouble when, in March 1925, she consented to examination at the London Hospital. She was then a healthy-looking woman of 28 years. She had a gross defect of vision, for which, since the age of 12, she had worn glasses; she could read well with her present glasses, which were: left, -15 D.; right, -13 D. Both kidneys could be felt. On the left side the kidney was distinctly enlarged, and its surfaces were studded with nodules, some of them as large as a cherry. The outline of the lower pole of the kidney was irregular. The right kidney was not enlarged. The liver could not be felt. Examination of the other systems showed nothing of importance except a raised blood-pressure (systolic 160, diastolic 98 m.m. of mercury). The urine was acid and contained a trace of albumin and a deposit of leucocytes; in cultures it yielded *B. coli*. Blood-urea, 0.030 per cent. Renal efficiency tests (phenolsulphonaphthalein and urea concentration test of Maclean) gave results falling within normal limits. X-ray examination of the urinary tract showed on the left side an opacity the size of a pea which, since it moved with respiration, was clearly in the left kidney. The bladder was normal at cystoscopy. A catheter was passed up the left ureter, and sodium bromide (16 c.c. of a 20 per cent. solution) was injected into the left renal pelvis, where it was retained. The skiagram showed slight enlargement of the renal pelvis and considerable elongation of the calyces, which were in places also narrowed. Although carried out with the utmost care, the pyelogram was followed by pain in the left loin, vomiting, and haematuria, and the patient, for so she had now become, had to stay in bed for a week. It is clear that *III. 7* suffered from polycystic disease of the kidneys, complicated by *B. coli* infection of the urinary tract.

*III. 8*, Cornelius L. (1892), husband of *III. 7*, said to be well.

*III. 9*, Samuel L. (1899), younger brother of *III. 7*, also suffered from polycystic disease of the kidneys. In June 1919, after a blow in the right side, he had severe and continued pain in the right loin without any haematuria. Being then on service he was admitted to a military hospital, where the right kidney was explored. The medical records, placed at my disposal by the courtesy of the Director-General of Medical Services, state that 'the kidney was found to be tubercular and was replaced'. After the operation acid-fast bacilli, 'much resembling tubercle bacilli', were found in the urine on one of the three occasions at which search was made. *III. 9* had no further trouble until March 1925, when a man on a bicycle ran into him and one of the handle-bars struck him in



the left loin. He felt at once severe pain in the left loin, and the same night vomited and passed blood in his water. A fortnight later, when the haematuria had ceased, he was admitted to the London Hospital under the care of Mr. Hugh Lett. The left kidney was greatly enlarged and slightly tender; distinct large nodules could be felt on its anterior surface, and the outline of its lower pole was somewhat irregular. The right kidney was slightly enlarged and its surface was probably nodular, but, owing to the scar tissue at the site of the old operation in the right loin, I could not be certain of this. The edge of the liver could not be felt. The systolic blood-pressure was 180, the diastolic 112 mm. of mercury. The urine was acid, of specific gravity 1010, and contained a deposit of pus and occasional red cells; no tubercle bacilli could be found, and there were no pathogenic organisms in cultures of the urine. The renal efficiency tests gave results within the limits of normal. Blood urea, 0.058 per cent. X-ray examination of the urinary tract showed great enlargement of the left kidney. The bladder at cystoscopy showed nothing of note beyond slight 'cystitis cystica' of the trigone. Clear urine was seen to come from each ureteric orifice. At different sessions pyelograms were taken. On the right side the 12 c.c. of sodium bromide solution injected did not nearly fill the pelvis, and all that could be said from study of the skiagram was that the right renal pelvis was enlarged. 36 c.c. of the opaque solution were injected into the left renal pelvis. The renal pelvis as a whole was greatly enlarged, but that part of the pelvis which joins the ureter was not at all dilated. The calyces were elongated and much broader than normal; their cup-shaped ends were normal. The patient was given medical treatment.

*III. 10*, Maud G. (1896), wife of *III. 9*, said to be well. *III. 11*, Leonard L. (1901), recently emigrated with his wife, *III. 12*, Lilian G., and children to Canada. *III. 11* always enjoyed good health, but was reported to be short-sighted.

*III. 13*, Ivy L. (1906), youngest daughter of *II. 2* and *II. 3*, had had up to March 1925 no symptoms beyond occasional backache, but she showed nevertheless signs suggestive of polycystic disease. Both kidneys were slightly enlarged, and in each the outline of the lower pole was irregular. The surface of the left kidney, which was the larger, was in parts distinctly nodular. The liver edge could be felt on deep inspiration, but the liver dullness was normal. No albuminuria; specific gravity of urine, 1026.

*III. 14*, John L. (1910), had always been well and on examination showed no signs of polycystic disease. His urine was normal. *III. 15*, two miscarriages of *II. 3*, included on the authority of her eldest daughter, *III. 1*, who, however, did not know when they had occurred. Of the children of *II. 4* and *II. 5*, *III. 22*, Thomas L. (1906), died of 'wasting disease' when six months old. *III. 16*, Eleanor L. (1898), *III. 20*, Alfred L. (1901), and *III. 23*, Frank L. (1912), showed no signs of polycystic disease of the kidneys, and all had normal urine. *III. 23* had defective sight and was wearing a strong concave lens on the left side and a plain lens on the right side. *III. 18*, Rosetta L. (1900), was not examined as she was pregnant. Individuals married into this family were: *III. 17*, Alfred W. (1894), husband of *III. 16*; *III. 19*, Jack B. (c. 1885), husband of *III. 18*; *III. 21*, Ivy D. (1904), wife of *III. 20*. These were reported to be healthy, apart from slight ailments. *III. 24*, Ernest L. (1898), eldest son of *II. 6* and *II. 7*, was healthy; his kidneys could not be felt and his urine was normal. His wife, *III. 25*, Bertha S. (c. 1895), was reported to suffer from jaundice, possibly due to gall-stones. *III. 26*, Sidney L. (1899), like his brother, *III. 24*, showed on examination no evidence of polycystic disease of the kidneys. *III. 27*, Alice C. (1898), wife of *III. 26*, stated that she had always enjoyed good health. *III. 28*, a male child born to *II. 7* in 1902, died of diphtheria when nine months old.

*III. 29*, Ethel L. (1904), was the first member of this family to come under observation. She suffered from attacks of pain and haematuria, which began in 1922, when she was 18 years old. The pain was confined to the left loin and left lumbar region and preceded the haematuria by one or two days. The attacks usually lasted from seven to ten days—though in the first attack she bled continuously for three months—and recurred at intervals of nine months. In the attacks micturition was frequent and urgent. Occasionally she had sharp pain across the back independently of haematuria. Towards the end of 1924 she began to suffer from 'turns' very like those her father II. 6 had had: she would become very drowsy and would then have a generalized 'hot flushing'; her whole body would get very red and she would frequently vomit. If her nose bled, as it usually did during these attacks, she would at once feel well again. The onset of these attacks coincided with the beginning of her first pregnancy. In 1925 she became a patient of Dr. Theodore Thompson's at the London Hospital, and later underwent urological investigations in the wards of Mr. Hugh Lett. She had congenital contracture of the third, fourth, and fifth fingers of each hand—of the 'hammer finger' type as described by Anderson (2). The contracture was most marked in the little finger, which, she said, had first shown signs of the condition when she was 10 years old. Both kidneys were palpable. The left was greatly enlarged, and on its anterior surface bosses could be felt, while the right was only slightly enlarged and not noticeably nodular. The liver was not palpable. The urine was acid and contained a trace of albumin and a deposit of pus; in cultures it yielded *B. coli*; specific gravity, 1016. X-ray examination of the urinary tract was negative. Blood-pressure: systolic, 110; diastolic, 80 mm. of mercury. Blood urea, 0.020 per cent. Renal efficiency tests gave results within normal limits. The bladder was normal at cystoscopy. A catheter was passed up the left ureter, and 7.5 c.c. of sodium bromide solution injected. In the pyelogram the renal pelvis proper was of normal shape and size, but the calyces were greatly elongated and in places narrowed, and were also widely separated from one another. No pyelogram of the right kidney was taken. A diagnosis of polycystic kidney disease was made and the patient was given acid sodium phosphate and hexamine, a form of treatment which she soon acclaimed. When last seen in April 1925 she was five months pregnant and was attending the ante-natal clinic of the London Hospital.

*III. 30*, Richard J. (1899), husband of *III. 29*. No information about his medical history. *III. 31*, Maud L. (1906), and *III. 32*, Hilda L. (1908), showed no signs of polycystic disease of the kidneys and had normal urine. *III. 33*, William D. (1898), eldest son of II. 8 and II. 9, was killed in the Great War. He was unmarried. *III. 34*, Henry D. (1900), died of convulsions when 9 months old. *III. 35*, Albert D. (1902), *III. 36*, Bert D. (1904), *III. 37*, Frederick D. (1907), and *III. 38*, Ernest D. (1909); these four boys I saw but was unable to examine. They had all the outward appearances of the good health they professed. *III. 39*, Stephen L. (1911), was jaundiced at birth. As a child and still, occasionally, in 1925 he had nocturnal incontinence of urine. The only abnormality found on physical examination was enlargement of the tonsils. The urine was normal. *III. 40*, Nellie D. (1912), showed no evidence of polycystic disease of the kidneys and had normal urine.

*III. 41*, Kathleen L. (1904), eldest child of II. 12 and II. 13, had defective sight even as a child, and in 1925 was wearing, and was suited by, a myopic correction of high degree. She complained of nothing, but the result of examination suggested that she probably had polycystic kidney disease. The left kidney was palpable in its lower third and had an irregular surface; it was not definitely enlarged. The right kidney and the liver could not be felt. The urine was acid and contained a cloud of albumin and a deposit of endothelial cells; no casts; specific gravity, 1015.



*III. 42*, Mary L. (1906), was short-sighted, but showed no signs of polycystic disease, and her urine was normal. *III. 43*, a miscarriage, for which *II. 13* was treated in a hospital [inserted on the evidence of the mother of *II. 13*]. *III. 44*, Annie L. (1909), suffered from short sight and poorly developed intellect. She showed no signs of polycystic disease of the kidneys. *III. 45*, Ellen L. (1910), was fat and healthy and showed no signs of polycystic disease of the kidneys, and her urine was normal. *III. 46*, a still-birth, which immediately preceded the death of *II. 13*. *III. 47*, a male (1904), only child of *II. 14* and *II. 15*, untraced.

#### *Fourth Generation.*

There is at present no evidence of the occurrence of polycystic disease of the kidneys in the fourth generation, which began in 1913 with the birth of *IV. 1*. I have examined 7 of the 18 individuals of this generation who were alive in April 1925: *IV. 1*, Conrad G. (1913), *IV. 2*, Annie G. (1915), *IV. 3*, Daisy G. (1918), *IV. 9*, Irene L. (1921), *IV. 14*, Gladys W. (1917), *IV. 15*, Alfred W. (1918), and *IV. 17*, Ernest L. (1920). In none of these could the kidneys be felt and none had albuminuria. The other members of this generation were reported to be well: *IV. 5*, George R. (1917), *IV. 6*, Lilian R. (1919), *IV. 7*, George L. (1919), *IV. 8*, Herbert L. (1921), *IV. 10*, Albert L. (1923), *IV. 11*, William L. (1924), *IV. 13*, Leonard L. (1921), *IV. 16*, Robert W. (1920), *IV. 18*, Alice L. (1922), *IV. 19*, Doris L. (1924), and *IV. 12*, a recent birth (1925). *IV. 16* was recovering from scarlet fever in Plaistow Hospital in March 1925, and Dr. MacIntyre, the medical superintendent, kindly informed me that *IV. 16* had no albumin in his urine and that his kidneys could not be felt. In addition to *IV. 16* three others, *IV. 2*, *IV. 14*, and *IV. 15*, gave a past history of scarlet fever. *IV. 4*, a miscarriage (1922).

In the foregoing report there occur many interesting facts about polycystic disease of the kidneys, but it is only necessary in this paper to summarize those which have a direct bearing on the question of heredity.

Eight members of this family have had polycystic disease of the kidneys, and two others are probably similarly affected. The affected ones are—in the first generation a female, *I. 1*; in the second generation four sons of *I. 1* (*II. 2*, *II. 4*, *II. 6*, and *II. 12*); in the third generation two females and one male (*III. 7*, *III. 29*, and *III. 9*). The two others probably affected are females of the third generation (*III. 13* and *III. 41*). The diagnosis of polycystic disease of the kidneys is based on post-mortem examinations in the cases of *I. 1*, *II. 2*, and *II. 12*; on examination of the right kidney at operation in the case of *II. 6*; and on clinical and special urological investigation in the cases of *II. 4*, *III. 7*, *III. 9*, and *III. 29*. In the last four cases the evidence is sufficient to make each one of them on its own merits a case of polycystic kidney disease. It is strong enough in the case of *III. 9*, whose right kidney was explored in a military hospital before he came to the London Hospital, to enable us to reject the diagnosis of 'tubercular disease' made by the army surgeon—or, at least, to reject any imputation of uncomplicated tuberculous disease implied by that term.

The girls, *III. 13* and *III. 41*, labelled 'probably affected with polycystic kidney disease', have as yet had no symptoms, and on their own merits they are not definitely cases of polycystic kidney disease. They are regarded as 'probably affected' because they present symptomless nodular enlargement of one or

of both kidneys. Excluding these two doubtful cases, it is seen that in three successive generations of a family comprising in all 42 individuals (the founder of the family, her 8 children, and 33 grandchildren), there occur at least 8 cases of polycystic disease of the kidneys; in other words, 19 per cent. of this family have had polycystic disease of the kidneys. This figure gives the lowest possible incidence of the disease, for it takes no account either of the two doubtful cases or of the six children who died in infancy. Some of the latter might, had they lived, have shown signs of polycystic disease of the kidneys—as indeed some of the younger apparently unaffected members of the third generation may still do.

In the three cases which came to necropsy, cysts were found in the liver as well as in the kidneys. In one other case (II. 4) enlargement of the liver was discovered during examination under an anaesthetic; this may have been due to cysts. None of the other cases showed enlargement of the liver on clinical examination, but it is quite possible that they had liver cysts, for Couvelaire (9) has shown that the liver cysts are frequently so small as to be visible only on microscopic examination.

Myopia occurred with great frequency in this family. From the case reports it will be seen that of the 42 individuals of generations I–III, seven were definitely, and for the most part strongly, myopic (II. 2, II. 4, III. 7, III. 23, III. 41, III. 42, and III. 44), and two others (II. 6 and III. 3) were probably myopic. Nine out of 42, or 21 per cent., is probably a conservative estimate of the incidence of myopia, since six members of the family died in infancy, and the surviving members of generation III were not subjected to routine ophthalmological examination. It may be concluded, therefore, that myopia is, like polycystic disease of the kidneys, hereditary in this family.

TABLE I. *Relationship between Polycystic Kidney Disease and Myopia.*

(In cases in which the presence of one or other of these conditions is only 'probable' the pedigree number is printed in *italics*).

	Cases.	Pedigree Numbers.
Polycystic kidney disease and myopia	5	II. 2, II. 4, <i>II. 6</i> , III. 7, <i>III. 41</i>
Polycystic kidney disease alone	4	II. 12, III. 9, <i>III. 13</i> , III. 29
Myopia alone	4	III. 3, III. 23, III. 42, III. 44
Polycystic kidney disease and defective vision of unknown origin	1	I. 1

The myopia and the polycystic kidney disease probably came from the same source, namely, I. 1; for of the founders of the family it is reported that, whereas I. 2 had good sight, I. 1 was blind in one eye. For obvious reasons the exact relationship of the two hereditary defects cannot be worked out accurately, but the data, so far as they are available, are given in Table I. From this it will be seen that polycystic kidney disease and myopia may both appear in the same individual or may occur separately. They are, therefore, produced by two distinct hereditary factors, which are clearly capable of free and independent assortment.

PART II. *Literature.*

In my search through the literature for cases of familial and hereditary polycystic disease of the kidneys, I have been considerably assisted by the paper of Dunger (11), in which were mentioned 13 of the cases recorded in the literature up to 1904. I have been able to collect altogether 23 cases, which will be considered in three groups according as they deal with polycystic kidney disease in one, two, or three generations. Most of the reports consider affected members of the family only, or contain merely passing reference to the unaffected members. These are inadequate for the detailed study of heredity in polycystic disease of the kidneys, and it is hoped that future reports will be accompanied by a full pedigree and description of the affected families.

*Three Generations affected.*

I have been able to find in the literature only one report which contains convincing evidence of the affection of three successive generations, and this is also the only family in which the normal as well as the abnormal members have been studied.

*Bull's Case.* In 1910 Professor Bull (6), of Oslo, published observations on a family, two generations of which suffered from polycystic kidney disease. One, and possibly another, member of the first generation and four of the second generation were affected. Bull himself examined twelve members of the third generation, all of whom were still under the age at which the symptoms of polycystic kidney disease usually appear, and he could find no evidence of the disease in them. Further information was forthcoming in 1914, when Paus (21) reported the discovery of polycystic kidney disease in a member of the third generation, a girl whom Bull had had no opportunity of examining.

The pedigree of this family is displayed in Fig. 2, and is described in the following pages. It is only complete up to the year 1909, but in two cases additional data have been added: the history of Thora Marie (III. 34) is brought by Paus's paper up to the year 1913, and is closed by Bull's account (8) of her final illness in 1918; and by another report of Bull's (7), the later history of Aagot H. (II. 21) is made available. For these last two references I am indebted to Professor Bull, who has kindly informed me that no other work has, so far as he knows, been done on this family since the publication of his first report in 1910. The family history appears to have been compiled with great care and accuracy, and reference to Bull's papers, which represent a valuable contribution to knowledge of the clinical as well as the hereditary aspects of polycystic disease of the kidneys, will supply many details omitted from the following abstract.

Inquiries into the history of this family were first made in connexion with Aagot H. (II. 21), from whom Bull removed an infected polycystic kidney.

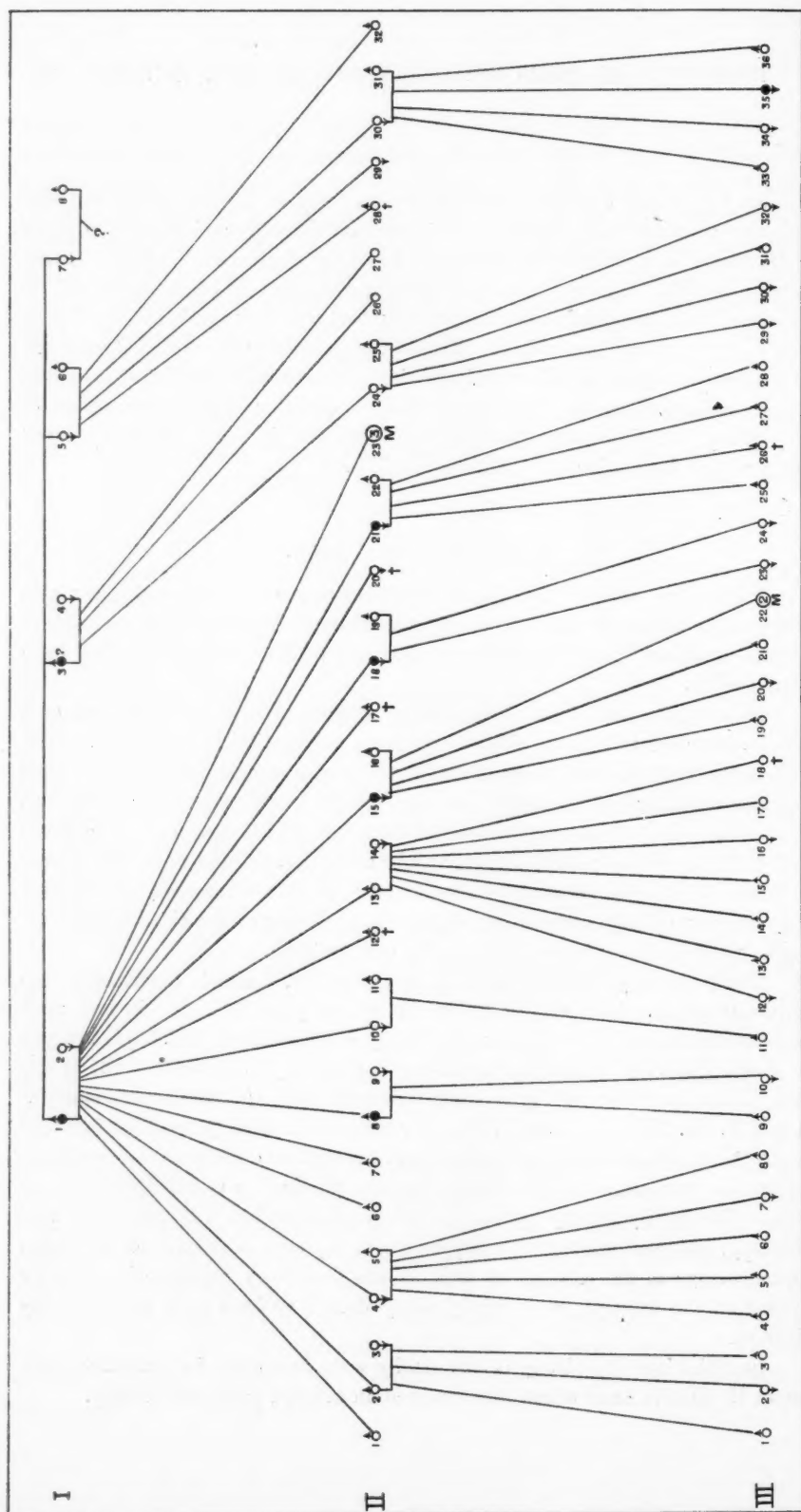


FIG. 2. Bull's Case (no consanguinity recorded).

*First generation.* This girl's father, Anders J. (1829), *I. 1*, died from uraemia at the age of 47 and post-mortem examination showed bilateral cystic kidneys. He lived at Frederikshald and was the father of seventeen children. His brother, Guldbrand J. (c. 1830), *I. 3*, died of apoplexy when 60 years old. It is possible that this man also had polycystic kidneys, for he suffered for many years from 'water trouble', attacks of pain in the left side, and a swelling under the left costal margin. *I. 5*, Marie M. (1833), sister of *I. 1* and of *I. 3*, died in 1876 from '? Apoplexy, ? heart disease'. *I. 7*, Lina Hansen R., a younger sister, died of cancer of the stomach and liver; her family could not be traced.

*Second generation.* The second generation includes four cases of polycystic disease (*II. 8, 15, 18, and 21*), all of them children of *I. 1*.

*II. 1*, John, the eldest child of *I. 1*, died of haemoptysis at the age of 25; he was unmarried. *II. 2*, Theodor (1857), went to live in America and had a family of three children; at the age of 52 he was believed to be well. *II. 4*, Marie P. (1861), married and had five children; she was presumably well in 1909. *II. 6* and *II. 7* died as young men, still unmarried: the one from phthisis, and the other from rheumatic fever.

*II. 8*, Anders G. J. (1865), appears to have suffered from polycystic disease of the kidneys. In 1905, when 40 years old, he began to have attacks of pain and haematuria which lasted several days and were usually brought on by exposure to cold, exertion, or 'the enjoyment of alcohol'. The pain was usually confined to the left loin, but on occasion radiated to the left groin and left testicle. The haematuria was severe in the first attack, and in one other attack in 1908; at other times it was slight or absent. With the attacks there came a feeling of weakness and faintness. Micturition was frequent and later became painful. In 1905 his doctor had told him that he had a kidney tumour. On examination in 1909 the left kidney was found to be considerably enlarged—its lower pole reached to the level of the umbilicus during deep inspiration. The lower half of the kidney was palpable, and was firm and slightly nodular. The right kidney could not be felt. The urine was slightly cloudy and contained albumin. The liver dullness was normal; at the liver edge could be felt a small nodule the size of an almond.

*II. 10*, Anna O. (1867), younger sister to *II. 8*, married and had one child. She was reported as well in 1909. *II. 12*, Haakon, died when 15 months old of an unknown cause. *II. 13*, also named Haakon (1869), was quite well in 1909; his kidneys could not be felt, there was no albumin in his urine, and he did not complain of pain. He was father of seven children.

*II. 15*, Magda J. (1870), died in 1909 at the age of 39 from polycystic disease of the kidneys and pulmonary tuberculosis. During the last fifteen years of her life she suffered from occasional attacks of abdominal pain and haematuria, sometimes associated with vomiting; and once, eight days before her second child was born, she had, for 24 hours, an attack of haematuria which was painless. In the attacks the pain was always on the left side of the abdomen, until in 1906, when it began to affect the right side. In April 1909 both kidneys were found to be greatly enlarged and nodular. Pleurisy set in during July 1909, and death occurred six weeks later. At necropsy the right pleural cavity was almost completely obliterated by dense adhesions, which were beset with tubercles, and the upper lobe of the right lung contained 'large tubercles the size of walnuts'. The kidneys were greatly enlarged (combined weight, 1,300 grammes) and consisted almost entirely of cysts (from pin-head to walnut size), which had a clear yellowish or chocolate-coloured content. Scarcely any trace of normal kidney tissue could be seen by the naked eye. (The microscopic appearance of the kidneys is described in detail by Bull;



it is identical with that usually found in polycystic kidneys.) The renal pelves were slightly dilated, the ureters and bladder were normal. The liver was free from cysts. A parovarian cyst was present on the left side, the genitalia being otherwise normal.

Of the younger children of I. 1, two, *II. 17* and *II. 20*, died in the second or third year of life, while two others, *II. 18* and *II. 21*, had polycystic disease of the kidneys. The last three conceptions of I. 2 resulted in still-births or miscarriages (*II. 23*). One of these, a premature child, was preserved in a Pathological Institute, but the specimen was unfortunately mislaid in the thirty years that elapsed before Bull's work began.

*II. 18*, Valborg F. (1874), fell and injured her right side when 26 years old. Immediately afterwards she had haematuria, and a few days later she had an attack of pain in the uninjured side of the abdomen. Between 1900 and 1905 attacks came on several times a year, but thereafter became less frequent until April 1909, when a severe attack occurred. The pain was situated in the left side and radiated to the left hip. It was accompanied by vomiting, shivering, and haematuria. During each attack the patient noticed a tender swelling under the left costal margin. At examination in April 1909 the left kidney was greatly enlarged ('almost as large as a coco-nut'), firm and tender, and its surface was nodular. The right kidney could be felt: while probably not enlarged, it was firmer than normal, and its surface was slightly irregular.

*II. 21*, Aagot H. (1877), was the first member of this family to come under Bull's care. On reaching maturity she had begun to suffer from a dull throbbing pain in the back and left side of the abdomen. The pain became acute at the end of 1908. In the following March a violent attack occurred and she was at once admitted to hospital. The temperature was slightly raised. In the left kidney region there was great tenderness and rigidity and a diffuse swelling. The right kidney was enlarged and prolapsed. Clear urine containing 1.3 per cent. of urea was obtained by catheter from the right ureter, while the urine from the left side contained pus cells and only 0.2 per cent. of urea. Having made a diagnosis of 'infected hydronephrosis', Professor Bull explored the left kidney. He found an infected polycystic kidney which he removed. The kidney measured 18 by 8 by 6 cm. and contained numerous cysts, up to the size of a walnut. One of the larger cysts was projecting into the pelvis of the kidney and had probably produced obstruction to the outflow of urine. In addition to the cysts there were numerous small abscesses on the surface of the kidney and streaks of pus were visible on the cut surface, in the portions of kidney tissue which could be seen between the cysts. Pus from the abscesses contained Gram-negative cocci and bacilli. In one calyx there was a calculus the size of a bean. The microscopic appearances, which are reported in detail by Bull, fully confirmed the diagnosis made at operation.

This left kidney was removed in April 1909. In the following August the patient began to have attacks of pain in the right side and in the intervals suffered with headache and dyspepsia. During an attack in July 1910, complete anuria occurred for 72 hours. The patient recovered from this, but had a further attack four months later, and died after five days' anuria. The investigations carried out during the final illness are interesting. In order to make quite certain that the anuria was not due to mechanical obstruction, Bull passed a catheter up the right ureter. No obstruction was encountered. In a few minutes turbid colourless fluid was seen to come from the catheter and 20 to 30 c.c. were collected in the space of half an hour. The fluid was neutral; it contained a trace of albumin and pus cells. The specific gravity was only 1000, and the murexide test (for uric acid) was negative. At the post-mortem examination the kidney, which weighed over 1,000 grammes, was found to be full of large and small cysts. The ureter was greatly dilated ('about a finger's



thickness') throughout the whole of its course, but nothing could be found, no stenosis or valve formation, to account for this curious fact. In the liver some scattered cysts of pin-head size were found beneath the capsule, and in one ovary there was a cyst the size of an almond.

*II. 24*, Karla O. (1872), the eldest child of *I. 3* and *I. 4*, married and had four children. She was quite well in 1909. *II. 26* and *II. 27* died of phthisis as adults. Of the children of *I. 5*, the oldest, Jorgen, *II. 28*, died from diphtheria at the age of 4. *II. 29*, Anna M. L. (1860), had apoplexy in 1898, and thereafter hemiplegia; her kidneys were palpable but not nodular, and the urine contained no albumin. *II. 30*, Thora Marie T. (1864), died at the age of 43 from disseminated sclerosis. For several years before her death she suffered from attacks of pain in the left side and pyuria. She had four children, one of whom, *III. 35*, had polycystic disease of the kidneys. *II. 32*, John, the youngest of the children of *I. 5*, died from malaria in the Congo when 27 years old.

*Third generation.* The third generation began in 1881 with the birth of *III. 4*. Thirty-five members are recorded by Bull (*III. 22* represents a miscarriage in 1906 and a premature birth early in 1909), and they appear on the whole to have been healthy at the time when his observations were made. Thirty-one of them were apparently quite well. The remaining four were: *III. 17*, unknown; *III. 18*, who died of congenital heart disease; *III. 21*, Rolf (1900), who had an operation for inguinal hernia in 1908 and later in the same year developed pleurisy; and *III. 26*, who died of tuberculosis when 9 months old. Bull examined personally *III. 2, 12-16, 19-21, 25, 27, and 28*, twelve in all. Of these, *III. 21* had a faint trace of albumin in the urine on one occasion, but his kidneys were not palpable. The remaining eleven gave negative results when examined for palpable kidneys or albuminuria (in some cases only one of these examinations was carried out).

*III. 35*, Thora Marie (1892), was shown later to have polycystic disease. She remained in good health until 1913, when, at the age of 21, she received an injury in the left lower abdominal region. Immediately after the accident she began to have pain in the left side associated with vomiting and haematuria. She was admitted to hospital twenty-four hours later, under the care of Dr. Paus. Paus found in the left kidney region a large firm swelling which extended downwards to within an inch of the iliac crest and inwards to the middle line. The urine contained a large amount of blood, but was otherwise normal. Paus made a diagnosis of ruptured kidney. At operation no rupture could be found, though there was some blood-clot beneath the fatty capsule, which was itself infiltrated with blood. Instead, the kidney was found to be greatly enlarged (about 25 cm. long, 12 to 15 cm. broad, and 10 cm. thick), and its surface was beset with numerous cysts, the size of a hazel nut. Reasoning that polycystic disease was a bilateral condition, and that, furthermore, he had had no opportunity of estimating the efficiency of the other kidney, Paus decided not to remove the kidney. It was well that he did so, for subsequent urological investigation showed that the right kidney was either missing or quite rudimentary.

After the operation the patient had from time to time attacks of haematuria, and in the spring of 1916 symptoms of uraemia intervened: headache, attacks of blindness, and fits. She died shortly afterwards. At necropsy the left kidney, which weighed 1,700 grammes, showed the typical appearances of polycystic disease. No right kidney could be found, but in its place was a nodule of tissue which was found on microscopic examination to contain renal tubules.

*Two Generations affected.*

*Thompson's Case.* Theodore Thompson (25) reported in 1903 the occurrence of polycystic disease of the kidneys in a father and daughter. The diagnosis was confirmed by necropsy in the first case and by operation of the left kidney in the second.

The father, J. J. (1850), began to have poor health in 1894, but was able to follow his trade until 1897, when he began to have diarrhoea, vomiting, and pain in the back. One month later he was admitted to the London Hospital in a condition of uraemia. He was very weak, but still conscious, and fibrillary twitchings of the muscles of the face and arms were observed. The urine was acid, of specific gravity 1010, and when boiled it became almost solid with albumin; it also contained a deposit of pus. There was no oedema. The patient became rapidly worse and died in general convulsions on the following day. Consciousness was retained to the end. At necropsy the kidneys were greatly enlarged (combined weight 6 lb. 1 oz.) and consisted almost entirely of cysts, of all sizes from a pin-point to a hen's egg. The right ureter was bifid in the upper six inches of its course. The left ureter was normal. The liver contained several cysts, of which the largest was  $\frac{1}{2}$  inch in diameter. The lungs were oedematous, the left ventricle of the heart somewhat hypertrophied.

The daughter, E. J. (1878), at the age of 23 had a short attack of haematuria accompanied by pain and faintness. This was at the beginning of 1901. Within a few months she began to notice her eyelids puffy of a morning and at times her skin would 'go yellow'. At the end of 1901, after an attack of sickness and diarrhoea, she began to have frequent, painful, and urgent micturition, and she passed water of a crimson or brown colour. Then followed pain in the right loin. She was admitted to the London Hospital in January 1902. The right lumbar region was tender on pressure, but no lump could be felt. In the left kidney region there was a very large mass with a smooth lobulated surface. The urine contained blood, a trace of albumin, granular casts, and pus. Tubercle bacilli were also found in the urine. The left kidney was explored by operation and was found to be polycystic; it was not removed. The patient was discharged from hospital one month later.

Thompson also reports the case of a woman, known to have polycystic disease of the kidneys, whose father had died of some kidney disease after an illness closely resembling that of the daughter. Both father and daughter suffered from haematuria and pain in the back, and the father had also a swelling of the abdomen.

*Borelius's Case.* The report of Borelius [cited by Dunger (11)] concerned a father, son, and nephew, all affected with polycystic disease of the kidneys.

The father, C. J. A., previously a healthy man, had pericarditis at the age of 70. Albumin was found in the urine during this illness. He recovered completely from the pericarditis, but after a short time he began to have indigestion and vomiting and became very thin. An ill-defined swelling was felt on the left side of the abdomen. The patient became cachectic and died in his seventy-first year. Post-mortem examination showed extensive pericardial adhesions and typical polycystic kidneys. There was little or no solid kidney tissue left, and the left kidney was larger than a foetal head. No cysts were found in the liver.

The son, C. A. A., when 38 years old, had apoplexy one day while mounting

his horse. He died on the following day. He had never had any symptoms suggesting kidney disease. The cause of death was a rupture of an aneurysm of the middle cerebral artery. Both kidneys were slightly enlarged, and on the surface of each were numerous cysts the size of a pea. There were no cysts in the liver.

The nephew, S. B., aged 51 years, had had attacks of severe renal colic for four years, and had on several occasions passed small stones in the urine. The urine contained albumin. A diagnosis of renal calculus was made. At operation the kidney was found to be definitely enlarged and to consist almost entirely of closely packed cysts, from pea-nut to walnut size or even larger. On the surface scarcely any normal kidney tissue was visible. No stones could be felt in the renal pelvis. The kidney was not removed. Shortly after the operation the patient had another attack of renal colic and haematuria. Subsequently the renal pains were less severe, but symptoms of bladder disturbance appeared, and on passing a sound vesical calculus was discovered. This man and a brother of his were both born with two thumbs on the right hand.

*Osler's Case.* Osler (19) reported the case of a man whose mother was also known to have had polycystic kidneys.

The mother had died in coma in 1882, and at necropsy polycystic kidneys were found. The son was 39 years old when he came under Osler's care. At the age of 34 he had had haematuria after an injury, and two years later had had haematuria again, this time after influenza. When Osler saw him he was complaining of occasional attacks of dyspepsia. The kidneys were greatly enlarged and there were nodular prominences on both. The urine contained a faint trace of albumin, but no casts. The liver was not enlarged. The arteries were thickened and the aortic second sound accentuated. Osler saw this man in 1902. In a later paper (20) he reported the subsequent history of the case: the patient had many attacks of haematuria, and finally died of uraemia in 1906.

*Dunger's Case.* Dunger (11) reported the case of mother and daughter with full macroscopic and microscopic descriptions of the kidneys of both.

The mother, a widow, aged 54 years, was admitted to hospital on account of severe headaches of six weeks' duration and failing sight. Paralysis of the left superior rectus was discovered and the fundi showed bilateral papilloedema and retinitis, with a single small haemorrhage on the right side. Nothing abnormal was observed on examination of the abdomen. The urine contained a cloud of albumin, occasional granular casts, and leucocytes. There was also an old-standing arthritis deformans of the fingers and left elbow-joint. After five uneventful weeks in hospital the patient suddenly had a stroke, and developed a right hemiplegia. She died in coma five days later. The immediate cause of death was haemorrhage from a ruptured aneurysm of the 'arteria corporis callosa sinistra'. The kidneys were typically polycystic: the right measured 17.5 by 16 by 6 cm. and weighed 365 grammes, the left was 15 by 10 by 5.5 cm. and weighed 760 grammes. The rest of the urinary tract was normal. Scattered through the liver substance were a moderate number of cysts, some as large as a walnut.

The daughter, aged 26 years, had no particular symptoms till shortly before death, when she suddenly became paralysed and soon afterwards expired. Necropsy showed that the immediate cause of death was a haemorrhage into the pons. The kidneys were sent to Schmorl's laboratory, where they were thoroughly examined by Dunger. The left kidney measured 12.5 by 6.5 by 5.5 cm. and weighed 195 grammes, the right was approximately the same size and weighed 232 grammes; both were beset with cysts of various size. The pelvis and calyces of the kidneys were moderately dilated. Both ureters were normal.

*Höhne's Case.* In 1896 Höhne (14) reported the case of mother and daughter.

The mother came to Höhne when she was 49 years old. Four years before she had had a right hemiplegia and aphasia, which had completely disappeared one month after its onset. For three years she had complained of dyspepsia and general ill health. In each lumbar region there was a nodular swelling. The urine contained a cloud of albumin, but no casts. The daughter was already known to have polycystic kidneys, and this suggested a similar diagnosis in the case of the mother. Confirmatory evidence was obtained by needling one of the nodules, for typical 'rosettes'<sup>2</sup> were found in the aspirated fluid. The patient died during anaesthesia for tooth extraction, and necropsy showed both kidneys to be equally enlarged and completely cystic. The liver also contained numerous cysts.

This woman had had five children. Three were quite healthy; one, a daughter, had died from kidney trouble when nine weeks old, while another daughter was shown by operation to have polycystic kidneys.

This girl had a cystic left ovary removed in her nineteenth year, and in the following year, as she still suffered from constant abdominal pain, the right ovary was also removed. During her convalescence pain returned on the right side and a nodular swelling was discovered in the right kidney region. The urine contained a trace of albumin, but no casts. The temperature rose, abscess was diagnosed, and the right kidney was explored. A cystic kidney was found and removed. It measured 11.5 by 6 cm. and was beset with cysts up to the size of a bean. The girl recovered.

*Steiner's Cases.* Steiner (24) demonstrated in 1899 two families suffering from polycystic kidney disease. The published record of the demonstration is, unfortunately, somewhat incomplete.

In the first family (Fig. 3, *a*) *I. 1* came under Steiner's care at the age of 52. He had had heart trouble for seven years and intermittent haematuria for four years. Polycystic disease was diagnosed clinically because both kidneys were greatly enlarged and distinctly nodular. The liver was enlarged and several hard prominences could be felt on its surface. The urine was of low specific gravity and contained a trace of albumin, many red cells, and casts. The patient died of uraemia at the age of 53. At necropsy the kidneys were found to contain cysts, many only of microscopic dimensions and others as large as a mandarine orange. The liver also contained cysts, some of which were very large. Of *I. 3*, sister of *I. 1*, Steiner merely says that she was suffering from polycystic kidneys. *I. 1* had several children. Of these, *II. 1*, a 10-year-old son, was demonstrated as having a cystic kidney on the right side. *II. 2*, 'several smaller children', suspected of having polycystic disease because of nodular, though small, kidneys and slight albuminuria.

The evidence presented in the second family (Fig. 3, *b*) is not quite so meagre. *I. 1*, aged 46 years, had had occasional haematuria for three years. His kidneys could be felt as large nodular masses extending on both sides from the costal margin to the pelvis. The urine contained blood, a large amount of albumin, and many casts; when free from blood it was of low specific gravity. *I. 3*, sister of *I. 1*, died of polycystic kidney disease at the age of 42 (specimens demonstrated). *I. 4*, a younger sister, aged 38 years, was demonstrated along with her brother *I. 1*. Her right kidney was greatly enlarged and had a nodular surface. The

<sup>2</sup> 'Rosettes', so named from their shape, are hyaline concentrically laminated colloidal bodies, not uncommonly found in the fluid content of the cysts. Contrary to the opinion of earlier writers they are not pathognomonic of polycystic disease of the kidneys, but may occur, as Dunger (11) has shown, in the cysts of chronic interstitial nephritis.

left was not so large, but was, nevertheless, larger than normal and had distinct nodules, some as large as a cherry, on its surface. I. 1 had several children. Of these II. 1, a boy aged 10 years, was demonstrated as having polycystic disease of the right kidney. II. 2, 'several smaller children', who had albuminuria.

*Crawford's Case.* Crawford (10) has reported a North Carolina family in which the incidence of polycystic disease is apparently very high. The evidence reported is, unfortunately, scanty.

Crawford's own case, Alex N., aged 34 years, had noticed for several years a slowly increasing abdominal swelling and had suffered occasional haematuria. Two large nodular tumour masses were felt on abdominal palpation. The urine contained albumin and red blood-cells. The clinical diagnosis of polycystic kidneys was supported by the family history. Operation by the transperitoneal route was undertaken for puncture of the cysts, some of which were as large as an orange. The patient died of uraemia two weeks after discharge from hospital.

The grandfather of Alex N., Ben N., died at the age of 77, apparently from abdominal tumour. Ben N. had seven children. Of these a son, John, father of Crawford's patient, had what was clinically polycystic disease; one daughter was found at operation to have polycystic disease, and two others were, it is

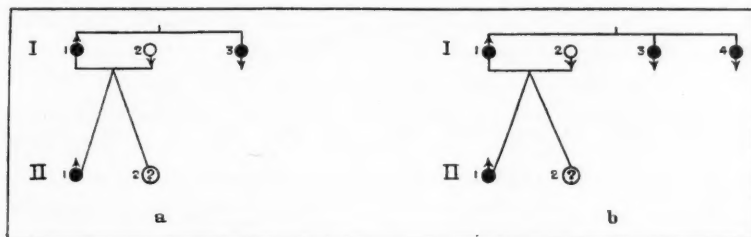


FIG. 3. Steiner's Cases (no consanguinity recorded).

stated, similarly affected. Several of the descendants, both children and grandchildren, of these three daughters of Ben N. are said to have had polycystic disease. Of John's family, four (including Alex N.) were shown by operation to have polycystic disease, while three others examined by Crawford had 'easily palpable kidney tumours'. While it is impossible to conclude from the evidence presented that either Ben N. or his great-grandchildren had polycystic disease, it is clear that the two intermediate generations were affected.

*Love and Richmond's Case.* In 1902 Love and Richmond (17) reported on a family residing in Paisley. The mother and three of her daughters had polycystic kidneys. Both of the authors have been kind enough to answer my inquiries about the subsequent history of this family, and from Dr. Richmond I have learnt many fresh facts which are included in the following abstract. The pedigree of the family, so far as it is known, is shown in Fig. 4.

The mother, I. 1, Mrs. J. senior (1836), began to have water trouble in 1890, when 54 years old, and two years later she was attended by Richmond for recurring attacks of pyuria. In 1896 pyonephrosis was diagnosed, and the suspected kidney was explored by Dr. Newman. 'Cystic kidney complicated by pyonephrosis' was found. The patient was 60 years old and very weak, so the kidney was not removed. She died three days later. There was no post-mortem examination.



The eldest daughter, *II. 1*, Mrs. H. (1861), had an infected polycystic kidney. Her case was described by Knox (16) in 1891. At the age of 29, after a chill, she suddenly had severe pain in the left side, accompanied by vomiting and the passage of porter-coloured urine. Frequency of micturition was increased. After 24 hours the haematuria ceased and the urine became milky. The attack lasted a fortnight, and after the first few days it was possible to feel a circumscribed swelling in the left lumbar region. The swelling gradually increased in size, and four months after the attack it was as large as a child's head and distinctly lobulated. The urine contained albumin, blood, and a little pus; specific gravity, 1018. The right kidney was not enlarged. At operation in November 1890 the left kidney was almost entirely composed of thin-walled cysts, up to 1 inch in diameter, and some of these contained pus. The kidney was removed and the patient did well. She enjoyed good health for many years and died in 1912, twenty-two years after the kidney was removed. Before the operation she had had two children and after it had two more.

*II. 3* and *II. 4* were twins. The boy, *II. 3*, died from nephritis following scarlet fever in his eleventh year. The girl, *II. 4*, Mrs. J., was first seen by Richmond in 1893, when she complained of a painless swelling on the left side.

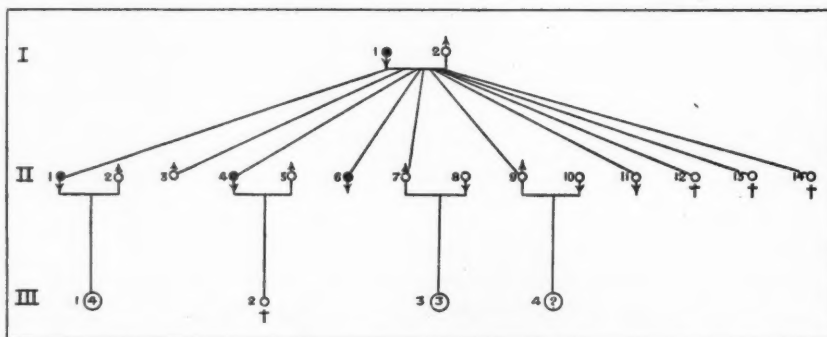


FIG. 4. Love and Richmond's Case (no consanguinity recorded).

The left kidney was enlarged, but the right kidney could not be felt. In July 1901, after a confinement, she had an abscess in the right leg. Examination at this time disclosed enlargement of both kidneys. The abscess was treated successfully by incision, but within a short time she developed oedema of the feet, ascites, and severe dyspnoea, and died in October 1901. At necropsy the kidneys together weighed 4 lb. 5 oz. The left kidney seemed almost entirely composed of cysts. The right kidney showed a considerable amount of normal kidney tissue on its exterior, but was also abundantly studded with cysts. The cysts contained clear fluid.

Another daughter, *II. 6*, Miss H., was in 1901 in the best of health, but Richmond was able to find a swelling, probably a cystic kidney, on the left side of the abdomen. His diagnosis appears to have been correct, for *II. 6* died in 1911, having been examined, during her last illness, by a well-known physician who diagnosed polycystic disease of the kidneys. Two sons, *II. 7*, Mr. W., and *II. 9*, Mr. J., had occasional albuminuria when examined by Richmond in 1901, but were otherwise at that time perfectly well. *II. 7* died in 1911 of an unknown cause. *II. 9* was alive in 1925, but was attending a doctor who had informed him that he had a 'floating kidney'. A younger daughter, *II. 11*, Miss S., was alive and well in 1925. *II. 12* and *II. 13* died of croup in infancy. *II. 14* died young, from chronic enteritis. The position of these last-mentioned three children in generation II is unknown.



## HEREDITY IN POLYCYSTIC DISEASE OF THE KIDNEYS 381

Little is known of the third generation. *III. 1*, the four children of *II. 1* and *II. 2*, were reported to be alive and well in 1925. Two of these children were born before *II. 1* had had her kidney removed, in 1886 and 1889 respectively, and the other two were born after 1890, the year of the operation. *III. 2*, the child of *II. 4* and *II. 5*, died of an unknown cause shortly after its birth in 1901. *III. 3*, the three children of *II. 7* and *II. 8*, of whom one, the eldest daughter, was said not to be well in 1925. *III. 4*, an indefinite number of healthy living children of *II. 9* and *II. 10*.

Other authors give passing reference to the occurrence of polycystic disease of the kidneys in two successive generations of the same family. Thus Rumpel (22) states that in two of his cases the condition could be regarded as familial. In one case the father and brother of the patient also suffered from polycystic kidneys, while in the other case the patient's father and uncle and the latter's son were affected. Both Rumpel's patients were males. In the case of Gayet and Bansillon (13), the mother, two daughters, and perhaps a son were affected.

### *One Generation affected.*

The cases illustrating affection of several members of one generation fall into two groups. One of these comprises the cases of polycystic kidney disease in the foetus or newly-born infant (congenital cystic kidney), and the other deals with polycystic kidney disease of the 'adult' type. The latter will be considered first.

*Beck's Case.* Carl Beck (3) reported the occurrence of polycystic disease of the kidneys in three sisters.

Beck's own patient, Miss S., aged 55 years, had suffered from dyspepsia for a year. She had a large movable tumour in the left kidney region. At operation the right kidney was only slightly enlarged and appeared to contain cysts only in its lower pole. The left kidney, a typical large polycystic kidney, was therefore removed. It weighed nearly 3 lb. The patient died of uraemia eleven days later. The eldest sister of Beck's patient also died of uraemia. At necropsy two enormous cystic kidneys were found. Another sister was found at the age of 40 to have a renal tumour. She died ten days after a large cystic kidney was removed. At necropsy, so the husband told Beck, degeneration of the other kidney was found.

*Sprent's Case.* Sprent's patient (23) belonged to a West Indian family of Scottish extraction which had subsequently scattered to all parts of the British Empire. The mother died at the age of 40 from some form of kidney disease. She had twelve children, of whom it was recorded that five (three males and two females) had polycystic kidneys, one other had some form of kidney disease, and the remaining six were healthy.

Sprent's patient, Miss M., was found at the age of 39 to have enlarged kidneys. Two years later she had definite haematuria. When 47 years old she again had haematuria. Sprent found that the right kidney was 'as large as a six months' pregnancy', while the left was 'about the size of a coco-nut'.

*Meyer's Case.* Meyer (18) reported the case of two brothers, aged 11 months and 2 years respectively. Both died of nephritis after diphtheria. At necropsy,

in each case, one kidney was about the size of a walnut and consisted of thin-walled cystic spaces, while the other kidney showed, in addition to hypertrophy, severe parenchymatous degeneration.

*Eisendrath* (12) mentions that he has seen a case in which five members of the same family had polycystic kidneys.

Of polycystic kidneys in the new-born (congenital cystic kidneys) Kaufmann (15) describes a small type in which the cystic kidneys are of normal size or but slightly enlarged, and a large type in which the kidneys assume enormous proportions. It is the latter type chiefly which appears in the cases of familial congenital cystic kidneys recorded in the literature. The cases are few and are for the most part inadequately reported; they are of greater value for a study of difficult labour than for a study of heredity in polycystic kidney disease.

*Wolff's Case.* In the case reported by Wolff (31 and 32), a woman gave birth within the short space of eleven months to two children affected with polycystic kidney disease.

The woman had previously had several normal labours. In January 1866 she was delivered of a still-born female child after a long and difficult labour. The delay was due to enormous kidneys, each of which measured  $7\frac{1}{2}$  inches by 4 inches. She came into labour again in December 1866, when Wolff extracted an asphyxiated male child which died shortly after delivery. This child had slight hydrocephalus and very large kidneys (6 inches by 4 inches) which showed on section 'cystoide degeneration'.

*Brückner's Case.* Brückner's patient (5) had, amid a large family of healthy children, two who were affected with congenital cystic kidneys and certain other malformations.

The woman and her husband were both healthy and well-built and came of families in which obstructed labour and malformed children were unknown occurrences. Altogether there were five normal confinements at which healthy children were born. At the fifth confinement twins were born, and one of these, a boy, died on the day after delivery of hæmorrhage from the umbilical cord and from the mouth.

At the third confinement, delivery was prevented by the great swelling of the child's lower abdomen, and was only accomplished by evisceration. The child had enlarged kidneys (each the size of a foetal head), hydrocephalus, short and crippled lower limbs, and accessory fingers. The seventh and last labour began in the eighth month of pregnancy and was very difficult. The child, which was still-born, had enlarged kidneys, hydrocephalus, short distorted extremities, and on each of these an accessory digit. The kidneys were sent to Virchow (27), who described them as being greatly enlarged (11 cm. by 6 cm.), excessively lobulated, and beset with numerous cysts, some as large as a cherry.

*Virchow's Case.* In this case reported by Virchow (28) a woman bore four children affected with polycystic disease.

The parents were both healthy, particularly the mother. She had, first of all, four normal children. The fifth and sixth labours were prolonged and difficult, in each case owing to distension of the abdomen of the foetus by very large hard tumours. Both children died shortly after birth, but no post-mortem examinations were made. The next birth ensued after a long and painful labour.

The child, which was still-born, showed at necropsy greatly enlarged kidneys in a condition of 'renal hydrops'. The urinary passages were quite patent. After this came a living child, normally born. The last child had a very distended abdomen. At necropsy the kidneys were as large as those of an adult and were beset with numerous small cysts.

*Singer's Case* (cited by Dunger (11)).

Singer's patient was a strong healthy woman. In the first confinement the presentation was a breech and one of the legs was pulled off during the attempts to deliver the greatly swollen abdomen. There was no necropsy. The second and third confinements were uneventful and the children well formed. In the fourth confinement great swelling of the child's abdomen again formed an obstruction to labour. At necropsy 'hydrops renum congenitus' was found. At the fifth and sixth confinements a healthy child was born on each occasion without medical aid. The seventh child, a female with a greatly enlarged abdomen, died five minutes after delivery. The eighth and ninth pregnancies gave two normal children. The tenth labour was again very difficult, and the child, which was still-born, had a very swollen abdomen. The eleventh and twelfth confinements were normal. In the thirteenth, labour was obstructed by the swelling of the child's abdomen, and delivery was only accomplished by evisceration. Examination at necropsy showed bilateral cystic kidneys.

*Wobus's Case.* In the case reported by Wobus (30) the mother was a native of Bosnia who had always enjoyed good health. She bore six children, of whom four had kidney trouble, and she had in addition one miscarriage.

At the fourth and sixth confinements a normal child was delivered. In each of the other four confinements labour was difficult and the child failed to survive. The first child had ascites, a thickened peritoneum, and kidneys of immense size completely joined by their lower poles. The second child had a papular eruption on the face, a thickened parietal peritoneum, and very large kidneys. The kidneys of the third child were large and cystic. The fifth child showed nothing abnormal except polycystic kidneys, of which the right weighed 40 gm., left 17 gm.

The above five cases are the only detailed reports of familial congenital polycystic kidney disease that I have been able to find in the literature, but two other examples are mentioned. Virchow (27) states that Schupmann had a patient who bore three children suffering from congenital cystic kidneys, and Couvelaire (9) cites Carbonnel as having observed polycystic kidneys in newly born twins.

### PART III. *Summary.*

In the East London family which I have described in the early part of this paper, certainly eight, and probably ten, cases of polycystic kidney disease have occurred in three successive generations, comprising forty-two individuals.

This observation does not stand alone, for from the literature I have been able to collect twenty-three examples of polycystic disease of the kidneys affecting more than one member of the same family.

In the Norwegian family described by Bull, certainly six, and probably seven, cases of polycystic disease of the kidneys occurred in three successive generations, comprising sixty individuals.

In eleven other families the disease was found in two successive generations.

In the remaining eleven families several members of one generation were shown to have polycystic kidneys.

Polycystic disease of the kidneys is one of the rarer affections of mankind. The number of cases seen by any one practitioner is small. At the London Hospital during the twenty-five years 1900-24, 389,773 indoor patients were treated, and of these only 79 had polycystic disease of the kidneys; that is to say, approximately only 1 in every 5,000 patients. These figures probably exaggerate the rarity of the disease, for they merely express the *clinical* incidence of the disease. But post-mortem statistics, which give a higher and more accurate figure, still indicate that the disease is a very uncommon one. Thus Naumann (cited by Dunger) found only sixteen examples of polycystic disease of the kidneys in the records of 10,000 necropsies.

Since polycystic disease of the kidneys is so rare, the examples of affected families collected in the foregoing pages cannot be accounted a coincidence, but can only be regarded as proof that, in these families, polycystic disease of the kidneys is an hereditary affection. And, therefore, if it be granted that polycystic kidneys constitute a single pathological entity, there is good reason to suppose that the disease is invariably hereditary.

But, it will be asked, how are we to reconcile this conclusion with the experience—which all clinicians must have had—of cases of polycystic kidney disease in which there is no family history of the disease? Of the occurrence, for instance, of polycystic kidneys in middle-aged or elderly individuals whose parents are still alive and well? As I have not studied the family history of a number of apparently 'isolated' cases of the disease I am unable to answer this question, but I can bring forward some facts which provide, at least, a partial explanation.

1. A patient may die of polycystic disease of the kidneys in such a manner that the correct diagnosis—or even a diagnosis of some unspecified kidney disease—would never be suspected by the most acute of clinical observers. The literature abounds with cases of this type; for example, the second of the cases reported by Whipham (29), and of those abstracted in this paper, the cases of Borelius and Dunger.

2. Polycystic disease of the kidneys may be present and yet never produce symptoms, even in individuals of advanced years. Thus Tow (26) has reported the case of a woman, aged 64, who, having died of pneumonia following operation for carcinoma of the breast, was found at necropsy to have polycystic kidneys. This condition of the kidneys had never been suspected in life and the usual examination of the urine before operation had revealed no abnormality. I have selected two further examples of symptomless polycystic kidney disease from the records of the London Hospital and report them in an appendix to this paper.

3. The 'intensity' of polycystic disease of the kidneys may vary in different members of the same family. For example, in the case of Borelius the son died of polycystic kidney disease at the age of 38, but the father, who was also affected,

lived to be 71. This question of variation in 'intensity' of the disease will be considered more fully in the subsequent detailed analysis of the hereditary process.

It is thus sufficiently obvious that cases of polycystic disease of the kidneys may easily be regarded as 'isolated' cases, when in reality the disease has occurred in other members of the family, but has been overlooked owing to errors of diagnosis or absence of symptoms. And those who would wish to refute the statement that all polycystic disease of the kidneys is hereditary in origin must produce extensive genealogical studies of 'isolated' cases in which is included evidence from post-mortem as well as from clinical examinations.

#### *Modes of Transmission.*

When we come to inquire the nature of the hereditary process in polycystic disease of the kidneys, it is necessary to bear in mind that the material at present available for analysis is very scanty and that great caution must therefore be exercised in drawing conclusions.

We are on firm ground, however, in concluding that the hereditary factor is not sex-linked. The disease affects males and females. Affected males when crossed with apparently normal females can produce affected males and affected females (for example, the first mating of generation II of the East London family, and the first mating in generation I of the family described by Bull). Affected females when crossed with apparently normal males can produce affected males (as in the mating in generation I of the East London family) or affected females (as in the mating in generation I of the family reported by Love and Richmond).

Can the disease 'skip' one or more generations? From perusal of Bull's case it might be thought that 'skipping' or latency did occur. In the pedigree the mother and grandmother of III. 35, who had polycystic disease of the kidneys, are marked as being unaffected. Yet it is quite possible that they were actually affected, for the mother, II. 30, had attacks of pain in the side and pyuria for some years before her death from disseminated sclerosis, and the grandmother, I. 5, died at the age of 43 from '? Apoplexy, ? heart disease'. Since this is the only example of possible latency that has so far come under notice, it must be concluded that 'skipping' or latency is not as yet proven. In view, however, of the undoubtedly large number of apparently 'isolated' cases of polycystic disease of the kidneys, it is probable that subsequent studies will show that latency does occur.

The available data are insufficient to admit of analysis on Mendelian lines; and even when more material has been collected there will still exist the difficulty of finding out exactly how many members of each family are really affected.

Although one cannot draw conclusions from such a small number of individuals, it is worth noting that, in the families now reported, the matings of



affected males or females with normal individuals were for the most part attended by a high degree of fertility.

*Variations in 'Intensity'. 'Anticipation.'*

Thompson (25) and others have found that polycystic kidney disease of the 'adult' type runs a fairly constant course: symptoms usually begin at or

TABLE II. *Showing the Variation in 'Intensity' of Polycystic Kidney Disease in Affected Families.*

(The pedigree numbers of cases of 'probable polycystic disease' are in italics.)

Author.	Pedigree Number.	Age (in years) at Onset of Symptoms.	Age (in years) at Death.	Remarks.
Cairns	I. 1	36	46	—
	II. 2	46	46	—
	II. 4	41	51	—
	II. 6	36	48	—
	II. 12	31	39	Died of bronchiectasis
	III. 7	25	—	<i>B. coli</i> infection of urinary tract
	III. 9	20	—	Symptoms brought on by injury
	III. 13	—	—	No symptoms at age of 19
	III. 29	18	—	<i>B. coli</i> infection of urinary tract
	III. 41	—	—	No symptoms at age of 21
Bull	I. 1	—	47	—
	I. 3	—	60	—
	II. 8	40	—	—
	II. 15	24	39	Died of pulmonary tuberculosis
	II. 18	26	—	Symptoms brought on by injury
	II. 21	31	33	Pyonephrosis of one kidney
	III. 35	21	26	Symptoms brought on by injury. Had only one kidney
Thompson	Father	44	47	—
	Daughter	23	—	Tuberculosis of urinary tract
Borelius	Father	70	71	—
	Son	38	38	—
	Nephew	47	—	—
Dunger	Mother	54	54	—
	Daughter	26	26	—
Höhne	Mother	45	49	Died under anaesthetic
	Daughter	20	—	—
*Love and Richmond	I. 1	54	60	Died after exploration of kidney
	II. 1	29	51	Infected kidney removed in 29th year

\* The other cases of this family are excluded owing to insufficient data.

slightly below the age of 40, and death occurs round the age of 50. The majority of cases here reported take this course, but reference to Table II will show that there are marked variations in the 'intensity'—if it may be so termed—of the disease in different members of the same family. And, furthermore, these variations are all in the same direction—the younger generations have their first symptoms at an earlier age, and die at an earlier age, than their



forbears do. In a number of cases the increase in 'intensity' of the disease can be explained, in part at least, by the presence of some complication, such as injury to the kidney, infection of the urinary tract, or the presence of intercurrent disease (see under 'Remarks' in Table II). Yet the increase in 'intensity' is found so constantly in the *later* generations as to suggest that it is not attributable to external causes, but that it represents an intrinsic part of the hereditary process in polycystic disease of the kidneys.

This phenomenon has been termed 'Anticipation'. It has been observed in other hereditary diseases, notably dystrophia myotonica (myotonia atrophica), in which the earlier generations, though free from dystrophic symptoms, suffer from cataract at an increasingly early age and are finally followed by a generation which exhibits, at a still earlier stage of life, all the cardinal symptoms of the disorder: myotonia, muscular atrophy, &c. (Adie and Greenfield (1)).

The most 'intense' form of polycystic disease of the kidneys is the type which is found in the foetus or newly born (congenital cystic kidneys), and on *a priori* grounds one would rather expect to find somewhere recorded the birth of a child with congenital cystic kidneys from parents affected by polycystic kidneys of the 'adult' type. Höhne's case, in which the mother, a sufferer from polycystic kidneys, had one daughter who died of 'kidney trouble' in the ninth week of life, cannot be said definitely to fulfil the requirements, and nowhere in the literature have I been able to find such a case recorded. On the contrary, the parents of children with congenital cystic kidneys appear to be extremely healthy individuals. For the present, however, no great significance need be attached to the apparent independence of the 'congenital' and 'adult' types of polycystic kidney disease in their familial and hereditary manifestations, for the recorded cases are few and incomplete.

While considering this question it is not inapposite to recall the views of the pathologists on the relationship of congenital cystic kidneys and polycystic kidneys of the 'adult' type. Modern pathologists incline to regard the two types as different manifestations of a single pathological entity, and Dunger (11) claims that the clinical distinction between them is more artificial than real, for he has been able to collect from the literature examples of polycystic kidney disease occurring at all ages between 28 hours and 27 years. Until comparatively recent years, however, there was considerable doubt as to whether the 'congenital' and 'adult' types of the disease were not in reality distinct pathological conditions (see Binney (4)).

#### *Associated Hereditary Anomalies.*

Hereditary myopia affected many members of the East London family, either alone or in combination with polycystic kidneys. Accessory digits occurred with polycystic kidneys in two of the children of Brückner's patient; the 'nephew' reported by Borelius was similarly affected, and so was his brother, whose renal condition is not recorded.

*General Considerations.*

The knowledge that polycystic disease of the kidneys is an hereditary affection may be profitably applied to other problems of the disease.

Considering, first, the pathogenesis of the disease, it is obvious that the view which would regard polycystic kidneys as an inflammatory or infective condition is no longer tenable. Between the other prevailing opinions, as to whether polycystic kidneys should be regarded as a tumour formation or as an error of development, it is impossible to decide, for each would be compatible with the heredity of the disease. But the fact that polycystic kidneys may be inherited *pari passu* with defects of known developmental origin, like the myopia which occurred in the East London family, strongly suggests that it, too, represents an error of development.

In the diagnosis of polycystic kidney disease, often a problem of great difficulty, the knowledge that the disease is hereditary is of great assistance. Since this work was begun a case illustrating this point has come to my notice. A middle-aged lady suffered from dyspepsia and was found to have an enlarged left kidney. She had been seen by an eminent clinician who made a diagnosis of 'hydronephrosis'. Twelve years before the patient's mother, who is still alive and well, had undergone nephrectomy for infected polycystic kidney. Consideration of this fact suggested a diagnosis of polycystic disease of the kidneys, a diagnosis which was subsequently confirmed at operation.

It is probable that in the future many facts of far-reaching importance will be discovered by those who are prepared to seek out and keep under observation families affected by polycystic disease of the kidneys. It will be possible to chronicle the life-history of the disease and to record many interesting clinical observations on the affected kidneys—the age at which they become palpable, their rate of growth, the length of time they exist without causing symptoms, the early symptoms, and similar interesting points. Material will be at hand to test the delicacy of the various renal efficiency tests. On this question it may be noted that one of the younger affected members of the East London family (III. 29) has symptoms which probably indicate a slight degree of uraemia, but her renal efficiency tests yield quite normal results.

It is not too much to demand that in future no case records of polycystic disease of the kidneys shall be considered complete unless the family history has been studied, and studied not by the cursory inquiry of routine clinical usage, but by accurate and complete investigation of the patient's genealogy.

I should like to thank the members of the medical and surgical staff of the London Hospital, in particular Mr. Hugh Lett, the Director of the Genito-urinary Department, and Dr. Theodore Thompson, for allowing me to study their cases, Professor H. M. Turnbull for providing the necropsy reports in the Appendix, and Professor William Bulloch for his advice about the preparation

## HEREDITY IN POLYCYSTIC DISEASE OF THE KIDNEYS 389

of pedigrees. I should also like to take this opportunity of thanking for their unfailing courtesy those physicians, surgeons, and family practitioners who, as recorded in the text, provided additional information about the East London family. In conclusion, it is with great pleasure that I record my indebtedness to Professor Bull of Oslo and Dr. Richmond of Paisley for their kindness in supplying me with further information about their published cases.<sup>3</sup>

### APPENDIX. TWO CASES OF SYMPTOMLESS POLYCYSTIC DISEASE OF THE KIDNEYS.

#### *Case I. Emily M., aged 44.*

Emily M., born in 1865, suffered from polycystic disease of the kidneys, though this was not discovered until she was examined at necropsy. From the age of 34 until her death ten years later she was four times a patient in the London Hospital; and her medical history is, therefore, comparatively complete, but it records no symptoms which can reasonably be regarded as being due to polycystic disease of the kidneys.

*Family History.* Notes taken in 1902 record that her mother had died suddenly of an unknown cause and her father had died of dropsy and asthma. She had nine brothers and sisters, of whom at that time two were dead. One of these had died of enteric fever. One surviving brother was suffering from 'heart trouble'.

*Personal history.* According to her own statements, Emily M. suffered between the ages of 7 and 13 years from dropsy, for which she was treated at some unknown hospital. She married and had no children. In 1897, when 32 years old, she noticed that she had an umbilical hernia, and in the following year she began to suffer from constipation and attacks of abdominal pain and vomiting. In 1899 she was admitted during a severe attack to the London Hospital, under the care of the late Mr. Waren Tay. The umbilical hernia was large and irreducible. An ice-bag was applied and enemata were given, but after several days, as the symptoms had not entirely disappeared, operation was performed. The intestinal contents of the hernia were freed from the wall of the sac and were replaced in the abdomen, the neck of the sac was closed, and a radical cure was performed. The operation was successful, and the patient was discharged wearing an abdominal belt.

She came into the hospital again early in 1902, on account of a lump in the breast. It was winter time and she was suffering from bronchitis, so she was discharged to await operation in the warm weather. In the following spring she was readmitted and a fibro-adenoma was shelled out of the left breast.

In 1901 she had fallen downstairs and afterwards noticed a small recurrence of the umbilical hernia. From that time onwards she experienced occasional pain in the scar, and with it vomiting. The hernia increased in size and the attacks became worse. In January 1909 she had a sudden attack of violent abdominal pain and vomiting, and was admitted once more to the London Hospital. She was very collapsed and had a large umbilical hernia, obviously strangulated. At an emergency operation the hernial sac was found to contain two feet of small intestine, of which five inches were quite gangrenous. The gangrenous portion was resected and an end-to-end anastomosis was performed.

<sup>3</sup> Since writing the above my attention has been drawn to some animal experiments which provide further evidence on the heredity of polycystic kidneys. H. J. Bagg (*Proc. Soc. Experimental Biology and Medicine*, New York, 1925, xxii. 271) has reported the occurrence of polycystic kidneys and of other kidney defects in several generations of the descendants of mice which had been exposed to X-rays.

The operation was completed by a radical cure according to Mayo's method. The patient died one hour later.

The urine of this patient was examined on four different occasions between 1899 and 1909. It always contained a trace of albumin and a macroscopic deposit of mucus; it was acid and its specific gravity varied between 1022 and 1030. At no time did the patient complain of urinary symptoms. The only other signs of note were a high-tension pulse and an accentuated aortic second sound. She was a fat woman: in 1902 she weighed about 15 stone, but she lost weight in the later years of her life, for at necropsy she weighed only 10 st. 9 lb.

*Summary of necropsy.* P. M. 56. 1909.

*Intestinal obstruction. Operation: resection of ileum and radical cure of strangulated umbilical hernia. Slight cardio-vascular hypertrophy. Polycystic disease of kidneys.* Slight hypertrophy of the heart (11½ oz.). Moderate general atheroma. Calcareous nodules in bronchial and mesenteric glands; fibrous pleural adhesions over left lung; fibrous adhesions between diaphragm and liver (3 lb. 2 oz.), and between diaphragm and spleen (11 oz.). Congestion of lungs. Mixed gall-stones in gall-bladder; no inflammatory thickening of wall or gall-bladder. Chronic granular inflammation of urinary bladder. Inspissated pus in cyst of right ovary and in termination of left Fallopian tube; fibrous perimetritis. Polypoid adenoma in pelvic colon. Fibromyoma in broad ligament. Very obese woman: height, 5 ft. 5 in.; weight 10 st. 9 lb. (Examination of head not permitted.)

The kidneys (left 16½ oz., right 14½ oz.) were greatly enlarged and consisted of a congeries of cysts between which very little solid renal tissue could be detected. The ureters were not stenosed. No cysts could be seen in the liver, pancreas, and suprarenal bodies.

*Microscopic examination.* The portion of kidney removed for examination was bounded on one side by a large cyst which extended from capsule to pelvis; on the other side a vertical series of smaller cysts occupied almost the whole of the renal tissue. Between these lateral cysts was an uninterrupted portion of cortex which measured 2 cm. in width and between 1.1 and 0.4 cm. in depth. Where this cortex impinged upon the lateral cysts there was a zone in which fibrotic glomeruli and atrophied tubules were embedded in a fibrous tissue infiltrated with lymphocytes and occasional plasma cells and eosinophil leucocytes. But in the greater part of the cortex there were only a few small areas of fibrosis, which contained fibrotic glomeruli and atrophied tubules. The renal tissue which was not affected by fibrosis was engorged; the epithelium of the first convoluted tubules and of the ascending limbs of the loops of Henle showed considerable albuminous degeneration and loss of nuclei; many collecting tubules contained hyaline casts. In the subjacent medulla there were several large and small cysts. The cysts were lined with a single layer of cubical or flattened epithelial cells. Several were filled with an eosinophil coagulum. The media of the interlobar and arcuate arteries was slightly hypertrophied. The intima of the interlobular, arcuate, and interlobar arteries was thickened by reduplication of the elastic stripe, and frequently showed a hyaline degeneration. The large veins were dilated.

The microscopic examination showed, therefore, that the kidney contained areas of parenchyma of considerable size which were free from the cysts and from the pressure effects of the cysts. But in respect of the amount of such tissue it is necessary to add that the portion removed for microscopic examination was specially selected because of the relatively large area which was free from cysts. The examination also gave evidence of slight cardio-vascular hypertrophy.

*Case II.* James O., aged 41.

James O. was suddenly attacked by violent abdominal pain on the afternoon of June 18, 1923, and on the same night was admitted to the London Hospital, under the care of Mr. Russell Howard. Clinical examination revealed unmistak-

able signs of perforation of a peptic ulcer. At an emergency operation a large perforated ulcer was found in the first part of the duodenum; the perforation was closed with difficulty and the abdomen was drained. The patient did not do well. In the second week of convalescence he developed broncho-pneumonia and suffered from increasing abdominal distension and vomiting. Severe ileus occurred on the eighteenth day and a jejunostomy was performed. The patient died shortly after that operation.

In the previous history of this patient it is recorded that he had had attacks of dyspepsia for nine months and had for some time suffered from constipation. Apart from that he had been perfectly well. His urine was examined twice while he was in hospital: on one occasion it contained a trace of albumin.

*Summary of necropsy.* P. M. 333. 1923.

*Broncho-pneumonia and abscesses in right lung. Operations: closure of perforation of chronic progressive peptic ulcer in first part of duodenum; jejunostomy. Polycystic disease of kidneys; cyst in liver. Focal fibrino-purulent peritonitis in neighbourhood of ulcer and within pelvis. Considerable dilatation of intestines. Congestion and acid digestion of lungs. Pin-head calcareous sub-pleural nodule in upper lobe of left lung. Fibrinous vegetation on aortic cusp of mitral valve. No hypertrophy of heart (10 oz.). Moderate general atheroma. Congestion of spleen (2½ oz.). Fibrous adhesions between diaphragm and right lobe of liver (3 lb. 12 oz.). Marginal haemorrhoids. Greatly wasted man: 5 ft. 11 in.; 7 st. 2 lb. 14 oz. (Examination limited to abdomen and thorax.)*

The kidneys (Pl. 17, Fig. 5) were greatly enlarged, the left measuring 23 cm. by 10.5 by 8 cm. and the right 21 cm. by 11.5 by 6.5 cm. Their combined weight was 4 lb. 4 oz. They appeared to be composed almost entirely of cysts. The cysts varied in diameter from 0.2 to 6 cm.; they were filled with watery fluid, which was usually clear and pale yellow but occasionally blood-stained. On section very little renal tissue could be detected between the cysts. The renal pelves were slightly dilated, and the calyces were considerably elongated. The ureters were neither dilated nor stenosed.

A cyst, which measured 2 cm. in diameter and contained clear fluid, projected from the under surface of the left lobe of the liver (Pl. 17, Fig. 6). No cysts were found in the pancreas.

*Microscopic examination.* The greater part of the two portions of kidney removed for microscopic examination was occupied by cysts of different sizes. These were lined with a single layer of cubical or flattened epithelium, and contained an eosinophil hyaline, or a reticular, or a granular substance, in which there were often red corpuscles, granules of pigment, and desquamated epithelial cells. One small cyst contained a glomerular tuft. In the portions of cortex between these cysts, there was a varying degree of interstitial increase, which implicated all but a few tubules. There were, however, few atrophied fibrotic glomeruli, and few atrophied tubules; the atrophied tubules often contained hyaline casts. Where there was no atrophy, the capsule of Bowman was almost always surrounded by fibrosis, but the glomerular tufts were large. The tubules were widened. The epithelium of the first convoluted tubules showed severe albuminous degeneration with loss of many nuclei, and the lumina contained a granular substance, in which remnants of necrosed epithelial cells could be recognized. The epithelium of the ascending limbs of the loops of Henle was affected in the same way, but to a less degree. The capsules of Bowman contained necrosed, desquamated epithelial cells and granular debris. A few of the discharging tubules in the medulla contained hyaline, or less frequently, granular casts. In one of the two portions there was a large intracystic papillary adenoma: doubtless a product of attempted regeneration. The medullary pyramid which was included in the section was concave. There was no appreciable hypertrophy of the arteries.

The microscopic sections showed very little renal tissue which was not occupied by cysts, and almost the whole of such tissue was fibrosed to different degrees.



## REFERENCES.

1. Adie, W. J., and Greenfield, J. G., *Brain*, Lond., 1923, xlv. 73.
2. Anderson, W., *The Deformities of the Fingers and Toes*, Lond., 1897, 44.
3. Beck, C., *Annals of Surgery*, Philad., 1901, xxxiii. 147.
4. Binney, H., *Modern Urology* (H. Cabot), Philad., 1924, ii. 685.
5. Brückner, C., *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1869, xlv. 503.
6. Bull, P., *Norsk Mag. for Lægevidenskaben*, Kristiania, 1910, 5. R. viii. 808.
7. Bull, P., *ibid.*, Kristiania, 1911, 5. R. ix. 457.
8. Bull, P., *ibid.* (*Forhandl. i Det med. sel.*), Kristiania, 1918, xvi. 113 and 126.
9. Couvelaire, A., *Annales de gynécol. et d'obstét.*, Paris, 1899, lii. 453.
10. Crawford, R. H., *Surg. Gynaecol. and Obstet.*, Chicago, 1923, xxxvi. 185.
11. Dunger, R., *Ziegler's Beiträge z. path. Anat. u. allg. Path.*, Jena, 1904, xxxv. 445.
12. Eisendrath, D. N., *Surg. Clin. of Chicago*, Philad., 1919, iii. 1057.
13. Gayet and Bansillon, *Lyon médical*, 1922, cxxxi. 771.
14. Höhne, E., *Deutsch. med. Woch.*, Leipz., 1896, xxii. 757.
15. Kaufmann, E., *Lehrbuch der speziellen pathologischen Anatomie*, 6<sup>te</sup> Aufl., Berlin, 1911, ii. 860.
16. Knox, D. N., *Glasgow Med. Journ.*, 1891, xxxv. 252.
17. Love, J. K., and Richmond, A., *ibid.*, 1902, lvii. 32.
18. Meyer, E., *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1903, clxxiii. 209.
19. Osler, W., *American Medicine*, Philad., 1902, iii. 951.
20. Osler, W., *Internat. Clinics*, Philad., 1915, i. 1.
21. Paus, N., *Deutsch. Zeitschr. f. Chirurgie*, Leipz., 1914, cxxx. 628.
22. Rumpel, O., *Arch. f. klin. Chir.*, Berlin, 1921, cxvi. 344.
23. Sprent, J., *Med. Journ. of Australia*, Sydney, 1924, i. 63.
24. Steiner, *Deutsch. med. Woch.*, Leipz., 1899, xxv. 677.
25. Thompson, Theodore, *The Pathology and Clinical Features of Generalized Cystic Disease of the Kidneys in Adults*. M.B. Thesis, Cambridge, 1903.
26. Tow, A., *Amer. Journ. Dis. of Children*, Chicago, 1923, xxv. 222-8.
27. Virchow, R., *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1869, xlv. 506.
28. Virchow, R., *Gesammelte Abhandlungen zur wissenschaftlichen Medizin*, Frankfurt, 1856, pp. 837-8 and 857.
29. Whipple, T., *Trans. Path. Soc. of Lond.*, 1870, xxi. 244.
30. Wobus, R. E., *Surg. Gynaecol. and Obstet.*, Chicago, 1918, xxvii. 423.
31. Wolff, W., *Berl. klin. Woch.*, 1866, iii. 269.
32. Wolff, W., *ibid.*, 1867, iv. 480.



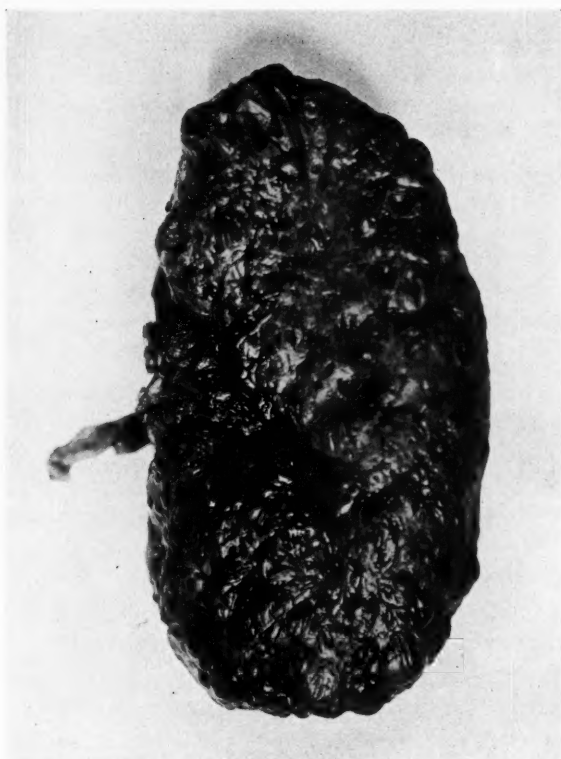
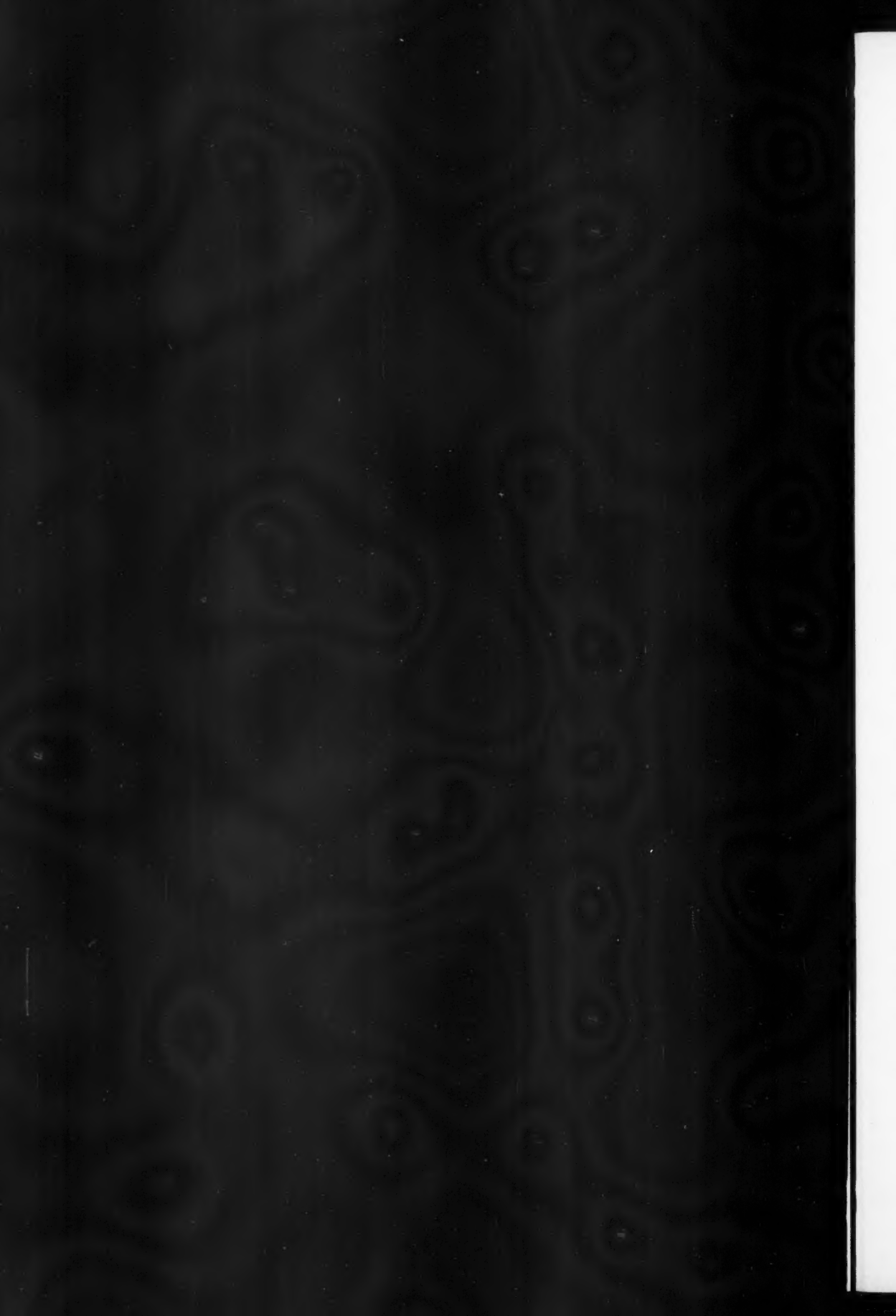


FIG. 5. The right kidney of Case II



FIG. 6. The liver cyst of Case II



## CRITICAL REVIEW

CHOLESTEROL IN HEALTH AND DISEASE<sup>1</sup>BY J. M. H. CAMPBELL<sup>2</sup>

(From the Department of Physiology, Guy's Hospital)

*Introductory.*

CHOLESTEROL was isolated by Conradi in 1775 and analysed by Chevreul in 1815, but at the beginning of the present century little was known about the part it played in any physiological or pathological process. According to Bunge, an authority at that time, cholesterol occurs in milk and in all animal and vegetable cells, and is perhaps an essential constituent of the food, because it is not known if it can be synthesized in the body; it may help to form gall-stones and is regularly excreted in the bile, whence it appears in the faeces; nothing is known as yet concerning its significance for any vital function (5).

As early as 1862 Flint tried to show the presence of cholesterol in the blood after feeding on large quantities of it mixed with fat, and soon after Picot demonstrated that the amount in the blood was increased in one grave case of jaundice (1), but the methods used were very unreliable. Little progress was made till 1909, when Windaus introduced an accurate method of estimating cholesterol (15); but before this Ransom had shown that it was able to prevent haemolysis by saponin (3), and the amount in the blood had been found increased in some cases of diabetes (Fischer (6)), and diminished in chlorosis (Erben (4)). Panzer (7) and Aschoff (9) had shown that the doubly refracting substance in the degenerated kidney was cholesterol esters, and Gardner had started his investigations into its physiology.

This early work was reviewed by Craven Moore (10) and by Dorée and Gardner in their first paper (13). During the last fifteen years an enormous amount has been written about cholesterol, and it is impossible within the limits of this article to review it at all completely. The aspect which is mainly dealt with here is the change in the cholesterol content of the blood and other organs in various diseases, and the relationship of cholesterol to haemolysis and sedimentation of the red cells is shortly discussed; what is known of its physiology is summarized to try and explain these changes. The subject has been reviewed in

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this Journal from a somewhat similar point of view (McNee, 1914 (43)), but though the main pathological facts had then been established, it is a little less difficult now to see some theoretical connexion between them and to paint, however dimly, a more coherent picture.

There is another aspect which must be mentioned. More than fifty years ago Hoppe-Seyler remarked that cholesterol and lecithin occurred in every cell, and about the same time Hermann suggested that alcohol, ether, and chloroform produced haemolysis because of their solvent action on these two bodies. Later this work was extended by Overton and Mayer, who developed the well-known theory of the cell surrounded by a semi-permeable membrane of lecithin and cholesterol, and during recent years much has been written about the factors determining the varying permeability of this membrane. An adequate discussion of this would require a separate paper, and it will only be referred to in trying to explain the variations in cholesterol in the different pathological states which are to be described.

#### *The Physiology of Cholesterol.*

There are still many gaps in our knowledge of the physiology of cholesterol, but the long series of papers by Gardner and his fellow workers is most valuable. Because they have hardly found their way into current physiological teaching, and the earlier conclusions have been somewhat modified by improved technique and increasing knowledge, it will be best to give a short sketch of them. Dorée and Gardner showed that cholesterol was not present in the faeces of herbivorous animals, the sterol there being derived directly from grass. It was present in the faeces of a carnivorous animal such as the dog, in which much less left the intestine in the faeces than entered it in the bile, so that some must have been reabsorbed from the alimentary tract (13).

The next question was to decide if the lost cholesterol was replaced by synthesis or from the cholesterol or phytosterol of animal or vegetable food respectively. They found that rabbits fed with cholesterol excreted some in the faeces, but half of what was given was absorbed and could be found in the blood (14). This confirmed by much more accurate methods the conclusions of Pribram (8).

At this stage Dorée and Gardner put forward their often quoted thesis which has been substantiated by much of their subsequent work: 'Cholesterol is a constituent of all cells, and when these are broken down it is not excreted as a waste product, but is utilized for the formation of new cells, a balance being maintained between the amount taken in the food and that lost in the faeces. One function of the liver is to break down dead cells, e.g. red corpuscles, and eliminate their cholesterol in the bile. After the bile has been poured into the intestine during digestion, the cholesterol is reabsorbed with the bile-salts, perhaps as esters, and carried by the blood-stream to various centres for rebuilding new cells' (14).

The object of the circulation of bile-salts is known, but it is not at all clear why cholesterol should be excreted in the bile and reabsorbed, instead of being carried directly by the blood-stream to the tissues for storage. From the close chemical relationship between cholic acid and cholesterol, it is probable that the cholic acid portion of the bile-salts is obtained entirely by the catabolism of cholesterol (29, 81). As the bile-salts play an important part in the digestion and absorption of food and are by no means completely reabsorbed, this makes it all the more essential that the supply of cholesterol should be conserved.

Continuing their work Fraser and Gardner found that in rabbits half of the cholesterol given in the food was excreted in the faeces unchanged, and that the other half appeared in the blood as free cholesterol. A smaller proportion of phytosterol, the corresponding vegetable compound, was absorbed and appeared in the blood as cholesterol (18). In the carnivorous animal it was more difficult to be certain of these effects because of the varying quantities of cholesterol occurring naturally in the food (17), but finally the results obtained in rabbits were confirmed for cats and dogs, and they showed that part of the cholesterol excreted in the bile was reabsorbed, the rest being reduced to coprosterol probably by bacteria (35).

At this time the question of the conservation of cholesterol seemed of special importance because Gardner and his co-workers had been unable to obtain any evidence of its synthesis in the developing egg (17), in the chicken (34), or in autolysis of tissue from the liver or spleen (109). Chauffard and Grigaut (30) had suggested that it was synthesized in the suprarenal, but this tissue was not investigated. Artom, on the other hand, believes that in autolysis of the liver the formation of cholesterol does take place, but is generally balanced by the destruction; when oleic acid was added the formation could be demonstrated (128).

In some experiments on the results of starvation, Ellis and Gardner found that the percentage of cholesterol in the liver, which was normally constant, was increased, as was also the percentage in the blood (21). They suggested that this was simply because the animal was living on its own tissues, i. e. on a high cholesterol diet. The percentage in the kidney, brain, and muscle was unaffected.

In their earliest experiments on man (who differs from the carnivorous animals by converting all the cholesterol of his faeces into the reduced form—coprosterol), Lander and Gardner thought that all the sterol lost could be accounted for by the amount taken in the food, and that it was only when there was a loss of weight, as in fever, that cholesterol was lost (28). But in 1921, with more careful analysis of the food-stuffs and observations on a larger number of subjects, they found that there was an excess of output over intake so that the body must be capable of synthesizing it (106). This may be because some is wasted by its reduction to coprosterol. In the infant, Fox and Gardner find that after the first few days rather more sterol is absorbed than is excreted, but that the difference is not sufficient to explain the amount stored in the growing child, so that synthesis must also take place (137). They still consider

the adequate supply of sterol in the diet and its conservation by the body important.

Put shortly, Gardner concludes that cholesterol given in the food appears in the blood both in herbivorous and carnivorous animals; that some of the cholesterol excreted in the bile is reabsorbed, since the output in the bile may be greater than the excretion in the faeces; and that the human body is able to synthesize it, since on various diets the output is found to be greater than the intake.

*Methods of estimating Cholesterol and its Occurrence in the Body.*

The most reliable way of estimating cholesterol is the digitonin method of Windaus (15), but it is not very convenient for clinical purposes as it requires a rather large amount of blood. Bloor and Knudson (54) and McNee (43) have shown that comparable though not quite such accurate figures can be obtained by the colorimetric method, which makes use of the play of colours produced by adding concentrated sulphuric acid and acetic anhydride. It was worked out by Grigaut (20, 26), and the actual technique most commonly used was developed by Myers and Wardell (69), and has recently been described in this Journal (119). A modification of this, which is rapid and accurate for small quantities, has been described (145).

The details of the methods have been most fully discussed by Gardner (107, 130, 138), who claims that the digitonin method only has an error of about 2 per cent., and that the colorimetric method is accurate to 5 per cent., if all the precautions he suggests are observed (107). Great experience is needed to reach this degree of accuracy, and there are several difficulties in the determination—the temperature conditions of extraction and the time allowed for the development of the colour requiring special care—difficulties which are probably responsible for many of the divergent results recorded. Bloor's method of extraction with alcohol and ether (52) gives higher results than the method of Myers and Wardell (69), which has been largely used.

To compare the results obtained in various diseases or to follow in detail the changes which take place after giving cholesterol by mouth, the amount normally present in blood is important, and the estimations which have been made show wide variations according to the method used. Klinkert (40) found an average value of 0.18 per cent., Widal (27) 0.18, Baemeister and Henes (41) 0.15, Bloor (52) by a rather different method, 0.21 in men and 0.23 in women, and in some cases examined by the author (148) the value ranged from 0.11 to 0.19, the average being 0.15. On the whole 0.15 to 0.20 per cent. may be taken as the normal range and 0.18 as the average, since Klinkert's results were all controlled by the more accurate digitonin method.

Cholesterol is equally distributed between the corpuscles and plasma, but in the corpuscles it is nearly all present uncombined, and in the plasma more than half is present as esters (see Table I, modified from Bloor and Knudson (54)).



As the amount present in the plasma is more variable in disease, this is generally estimated.

TABLE I.

*Distribution of Cholesterol in Blood.*

	Whole Blood.	Plasma.	Corpuscles.
Total quantity in grm. per 100 c.c. blood	0.18	0.09	0.09
Ester of cholesterol	0.06	0.05	0.01
Free cholesterol	0.12	0.04	0.08

Cholesterol also occurs in the bile, in large amounts in the white matter of the nervous system, especially the brain, in the suprarenal cortex, and in smaller amounts generally associated with lecithin in practically all the cells of the body as well as in various pathological conditions. In the brain it occurs mainly as free cholesterol, and practically nothing is known about its function, though certainly it is not a mere store of reserve material, for in starvation the brain is one of the organs which suffers very little loss of weight.

In the bile, too, it occurs as free cholesterol, and McNee has shown that in general the percentage in the bile varies with the amount in the blood (43). It is not at all clear why cholesterol should appear in the bile, if its conservation is important and much of it has to be reabsorbed. From the intimate connexion with fat in later stages of metabolism it seems possible that in some way it may help in the absorption of fat, but of this there is no direct evidence. McMaster found that when the diet was rich in cholesterol the percentage of it in the bile was also increased, as it was in the blood, but in starvation when the percentage in the blood was increased the quantity excreted in the bile was decreased, although the concentration was higher (144). This rather confirms Gardner's view of the conservation of cholesterol of the body.

Early observers were struck by the large amount of cholesterol present in the suprarenal cortex, and in a large number of pathological conditions this has been found to vary with the amount in the blood. Thus it is greatly increased in starvation (114) and in the latter months of pregnancy (24, 30). More recently Chauffard has shown that in a large number of different diseases the cholesterol content of this gland and of the blood vary together (149), and the view has been put forward by him and others that it is the organ responsible for the manufacture of cholesterol. The only definite evidence in favour of this is the very high content of cholesterol in some adenomata of the cortex and the claim that removal of the suprarenal causes a fall in the cholesterol content of the blood (124) (see later).

The known facts can be equally well explained by supposing that the content of this gland depends on the amount available in the blood. This view was supported by Landau (36) as the result of the examination of a large number of suprarenals, and he and McNee (43) have brought forward some direct evidence in favour of this by showing that after feeding with cholesterol

the amount of it in the suprarenal cortex was increased. Recently Joelson and Shorr (152) found that in every case removal of the suprarenals led to a rise in the cholesterol content of the blood. They discuss the discordant results of previous workers and suggest that the internal secretion of the suprarenal controls the level of cholesterol in the blood as insulin does the blood-sugar. Their attempts to prove this by injections of adrenalin were not successful. Steinitz (153) in studying the effect of long-continued injections of adrenalin on the blood-vessels of rabbits also found that these injections had no effect on the amount of cholesterol in the blood.

*The Relationship of Cholesterol to Fat and Lecithin.*

It is difficult to discuss the functions of cholesterol further without some reference to the other lipoids and certain general aspects of fat metabolism. In his recent Croonian lecture on the rôle of fats in vital phenomena, Leathes dealt with the importance of cholesterol and lecithin, pointing out that the old view of the fats merely as a *depôt* of reserve material must be abandoned (161). The tissue fats differ from the storage fats in three important particulars. The fatty acids differ in being more unsaturated; they are combined differently, e.g. with cholesterol or phosphoric acid instead of glycerin, the lecithin portion in many organs being three-quarters of the total lipoids; and even in starvation they tend to remain constant. Leathes urges that the fats must be looked on as just as essential in the structure of protoplasm as the proteins.

The various tissues differ in the ratio of cholesterol to fatty acid, but this remains fairly constant for the same tissue in different species (37). Those with the most cholesterol have the greatest power of holding water by imbibition, and in starvation when the amount of cholesterol relatively to the fatty acid is increased, the capacity for imbibition of water is also increased. These facts may be of importance in the explanation of some types of oedema, and it is interesting that in hydraemia following certain diuretics the percentage of cholesterol in the blood is increased, while that of the other constituents is of course diminished, and that the cholesterol content is diminished when the blood is concentrated (143).

The theory of Overton and Mayer of the cell surrounded by a semi-permeable membrane of lecithin and cholesterol explains a vast number of observed facts and cannot be dismissed lightly, but, as Leathes points out, it is difficult to reconcile with the free permeability of nearly every cell to water through a membrane which is by definition one that gives passage to everything soluble in lipoids. It is not possible here to follow out the fascinating physico-chemical theories which Leathes applies to the cell, especially the definite conception of the oblong molecules of fatty acid arranged vertically at the water surface. The experiments of Langmuir (65) and Adam (90) on fatty films and of Leathes (l. c.) on lecithin and cholesterol suggest great possible advances in the near future along these lines.

In a recent review on fat transport in the animal body (116) Bloor has summed up present opinion as follows: In the intestine fat is completely hydrolysed and passes through the epithelial cell-wall as soap and glycerol, and the old view of Schafer (117) that the leucocytes are partly responsible for the transfer to the lacteals is strongly supported by Clark and Clark (58), who showed that fat injected into the tadpole's tail was rapidly removed by leucocytes. The reaction was not merely an inflammatory one, for mineral oil was not removed in the same way. Only 60 per cent. of the fat absorbed can be traced to the lacteals, and though direct evidence is still not available it is probable that some of the remainder is absorbed directly into the blood. In the lacteals it is mainly in a finely divided suspension (particles about  $1\mu$  in diameter).

This same process of hydrolysis and resynthesis may take place wherever it is necessary to transfer fat across a cell membrane, but lipase is only present in very small amounts in most parts of the body, and is almost absent in some tissues actively concerned in fat metabolism. On the other hand, Porter (56) has shown that ferments capable of splitting or building up lecithin are present in much larger amounts, especially in these tissues.

Leathes originally suggested that lecithin was a stage in fat metabolism, and direct evidence of this has been brought forward by Bloor, who showed that after feeding with fat there was an increase in fatty acids in the blood and a parallel increase in lecithin (of 10 to 35 per cent.) (48); that the increase in fatty acids took place in plasma and corpuscles; and that the increase of lecithin was only slight in the plasma but very considerable in the corpuscles; from all of which he concluded that the blood corpuscles take fat from the plasma and transform it into lecithin, much of the fat absorbed being treated in this way (52).

Some old observations of Cohnstein and Michaelis (2) on this point almost seem to have been forgotten. When air was passed through defibrinated blood three-quarters of the fat present as chyle was changed into some form soluble in water. It was due to the haemoglobin, for it occurred in laked blood but not in serum. They therefore suggested that the fatty infiltration which was liable to occur in anaemia was due to the smaller amount of haemoglobin. Recently these observations have been extended by Wilstätter (123) and Robinson (139), who found that haemoglobin or haematin, but not haematoporphyrin, was able to catalyse the oxidation of linseed oil. The concentration of inorganic iron needed was enormously greater.

Whatever the mechanism, the change from fat to lecithin seems to occur readily under various conditions in the body.

#### *Cholesterol and Lipaemia.*

In addition to the general relationship of fat, cholesterol, and lecithin as outlined by Leathes, and this special metabolic connexion of fat and lecithin, there is a close connexion between fat and cholesterol which is best exemplified

by the phenomena of lipaemia. What is known about alimentary lipaemia will be described rather fully, because in its main features it resembles the lipaemia which may occur in various diseased conditions—practically the same group of diseases as those in which an increased amount of cholesterol occurs in the blood.

Various observers have confirmed Gardner's finding of an increased cholesterol content of the blood after taking it in the food, and some have found that a meal containing fat produces a similar result (31, 41, 47, 80). Eggs, butter, and meat are specially effective in producing this increase (70), and though ordinarily the change in cholesterol is not very great, after feeding horses on brain tissue for a long period the increase may be 60 per cent. and may last for a long time (93).

What is really more important for our present purpose is the change in the various lipoids of the blood after feeding on fat. In most animals feeding with large amounts of fat can produce a visible lipaemia, and this if continued is associated with an increased amount of lecithin and often of cholesterol in the blood (98). There is general agreement about the increase in fat and lecithin in any lipaemia following the ingestion of fat, but some disagreement about the increase of cholesterol. In some experiments no increase of cholesterol in the blood after feeding with fat has been found; for example, the present writer found that before breakfast his plasma was clear and contained 0.15 per cent. cholesterol, and three hours after breakfast of four eggs, fat bacon, and a double ration of butter the plasma was quite cloudy but the cholesterol content was unchanged.

But various workers have already been quoted as finding an increase in cholesterol after feeding on fat, and the discrepancy is probably explained by the experiments of Iscovesco, who has shown that the increase in cholesterol occurs later than the increase of fat and lecithin (33). Bloor has also found in various types of lipaemia that the fat increases first, then the lecithin, and finally the cholesterol, and he suggests that this is why it has not been obtained by all workers, and in some of his own experiments when the blood samples were taken shortly after the cholesterol was given. Knudson (76) has shown that feeding with neutral fat increases the cholesterol esters (especially in the plasma), and that feeding with cholesterol or its esters causes an increase in free cholesterol (in both plasma and corpuscles). With continued cholesterol feeding, as with fat feeding, a true lipaemia may also be produced, the fat and lecithin content of the blood being increased as well as the cholesterol (71).

Under ordinary conditions Bloor has found that the lipid content of the blood is as follows (52): Fat is present in very small quantities in the plasma and practically absent in the corpuscles, and cholesterol and lecithin each form about one-third of the 'total ether-soluble' lipoids, the lecithin being less in women. The total fatty acids are less in the corpuscles than in the plasma (possibly because of the small amount of cholesterol esters in the former), the total cholesterol is about the same, but the lecithin in the corpuscles is about

twice as much in the corpuscles as in the plasma, so that the lecithin to cholesterol ratio is about two in the corpuscles and unity in the plasma. The importance of this ratio will be seen later.

In persistent lipaemia, however produced, there is always an increase in fat, lecithin, and cholesterol. In lipaemia following diabetes or haemorrhage (see later) Bloor has shown that in their main features they are identical with alimentary lipaemia (98), i.e. the fat increases first, then the lecithin, and finally the cholesterol, and the greatest increase is in the fat and the least in the lecithin, so that the ratio of lecithin to cholesterol, which remains constant in a large number of conditions, is decreased (52).

In a large number of pathological conditions without lipaemia Bloor found that the change in the amount and ratio of the various blood lipoids was greater than in the 'total ether-soluble' lipoids, and that often the total fatty acid was increased and the lecithin decreased. He interpreted this as a diminished production of lecithin from fatty acid and looked on it as a failure in fat metabolism. Generally the lecithin to cholesterol ratio remained constant, so that the cholesterol was also reduced.

On the other hand, in the diseases where lipaemia occurs, the changes were as already described, and the lipoids were all increased, the cholesterol more than the lecithin. He also investigated the changes in the phosphorus content in experimental lipaemia and found, as might be expected, that the lipid phosphorus was mainly affected and might be five times as much as the normal, but sometimes this was accompanied by an increase in the inorganic phosphate; the organic (acid-soluble) phosphorus in the corpuscles was very constant and there was very little of this form in the plasma (97).

The changes in cholesterol during starvation can be explained most readily by supposing that they are associated with the increased fat metabolism. During starvation in rabbits Rothschild (49) found an increase in the cholesterol in the blood, and Okuneff (114) found the amount in the suprarenal cortex greater than normal, no drop occurring in the most severe starvation. This may be due to the increased circulation of lipoids in the blood when a greater proportion of fat is used in metabolism, as suggested by Gardner. Asada (127) found that with shortage of food which was normally constituted the fat decreased and the cholesterol increased, but that on a vitamin-free diet the fat and cholesterol varied together, both being spared as long as carbohydrate was available. In castrated animals Lemeland (104) found the same changes as in starvation, and this may be associated with the diminished metabolism and increased tendency to the deposition of fat.

Evidence has been given that the increased lecithin in the blood is synthesized from the fat, and that the red blood corpuscles play an important part in this. Bloor supposes that fat is converted into lecithin because it is a convenient form for water transport, whereas the soaps, the other easily soluble form, have undesirable effects on the cell membrane. The fact that lecithin and cholesterol are found so constantly in close association in the body, and that as regards



haemolysis there is some definite antagonism between them, suggests that this is the reason why cholesterol is increased as well as lecithin in lipaemia (Bloor).

The most natural explanation of the fact that the cholesterol and lecithin are also increased in the blood, when the fat is increased owing to the larger amount being absorbed, is that both are a stage in fat metabolism. The evidence that this is so in the case of lecithin is now very strong. It is not quite clear if Bloor favours this explanation in the case of cholesterol, because, although he speaks of the production of cholesterol esters from fats, he suggests that the cholesterol is generally increased after the lecithin to keep the ratio constant. In lipaemia this does not occur and the cholesterol is increased more than the lecithin. In some ways it seems more likely that cholesterol is also a stage in fat metabolism.

While its constitution is still unknown this may seem an improbable suggestion, but it explains what is known of alimentary lipaemia, and as the various facts about cholesterol are reviewed it will be found to provide the most simple hypothesis. Cholesterol can be synthesized in the animal body and the amount in the blood increases after feeding on fat. This makes it reasonable to assume that fat may be turned into cholesterol, and there is some evidence that it may be synthesized from oleic acid (89). Artom has shown that in the autolysis of liver tissue the production of cholesterol can be increased by the addition of oleic acid (128). Nothing is known about the chemical constitution of cholesterol which makes it improbable that it is a combination of the terpene ring ( $C_{10}H_{16}$ ) with some body closely related to oleic acid.

The general conclusion is that a diet containing excess of fat or cholesterol tends to produce alimentary lipaemia. When taken in the form of fat the fat will first be increased in the blood, then the lecithin, and, after a long interval, the cholesterol. When the lipaemia disappears the change takes place in the same order, as the fat diminishes first, then the lecithin, and finally the cholesterol. The greatest increase is in the fat and the least in the lecithin, so that the ratio of lecithin to cholesterol will be diminished. The order in which these changes in the various lipoids takes place suggests that fat is the most easily metabolized, and that cholesterol is the most stable form.

The simplest explanation of these facts is that cholesterol and lecithin are both stages in fat metabolism, and this will fit in best with the various pathological changes to be reviewed. But it remains unproved, and it may be that the cholesterol is increased in an attempt to keep the ratio of lecithin to cholesterol as constant as possible.

#### *Cholesterol in the Blood during Pregnancy.*

Apart from starvation and feeding on fat or cholesterol, pregnancy is the only other physiological condition where changes occur. Hermann and Neumann (23), and shortly afterwards Chauffard, Laroche, and Grigaut (25), found a retention of cholesterol during the last three or four months of



pregnancy, the amount in the blood averaging 0.25 per cent. or sometimes nearly double this (25, 40); the increase lasted for a short time after confinement, the excess being got rid of by excretion in the milk probably to make up for the very low cholesterol content of the blood of the child at birth (25). As we have seen, there is a close connexion between fat and cholesterol metabolism, and the increase during the latter part of pregnancy is probably due to the anabolic changes which provide the fat needed for the foetus and subsequently for the milk.

That the increased heat-production during the latter part of pregnancy is considerable and may well account for changes in the type of metabolism has been shown recently by Sandiford and Wheeler (155), who found that it amounted to 25 per cent. of the basal metabolism, although calculated according to the active protoplasmic mass of the mother and foetus, it appeared to be unchanged. This is in addition to the extra anabolic changes for the growth of the foetus and other structures. It is possible that the acidosis found in the later months of pregnancy is also of importance. It can hardly be coincidence that three such different conditions as pregnancy, diabetes mellitus, and nephritis also tend to produce acidosis and a high cholesterol content of the blood unless there is some connexion between these two factors. This will be discussed later.

The suprarenals share in the excess retained during pregnancy and become laden with cholesterol (24, 30). McNee found the amount in the bile enormously increased during pregnancy (43). In the early stages of pregnancy the amount in the bile is low, presumably during the period of retention of cholesterol in the maternal and foetal bodies, but later it increases and after parturition the retained cholesterol is got rid of in the milk and in the bile, which is two or three times as concentrated as normal and will often deposit cholesterol crystals (Pfibrum (126)).

According to a recent review on milk production (131) the fat is produced from the phospho-lipins circulating in the blood—further evidence that lecithin is the currency for fat. And Bloor (97) in experimental lipaemia found, as would be expected, that the lipid phosphorus was mainly affected. The cholesterol content of the corpus luteum is very high and undergoes cyclical changes, being lowest in the haemorrhagic and highest in the regressive stages (30). Recently Shiskin has shown that there is a premenstrual rise in the cholesterol content of the blood (160).

These, the main facts which are known about the physiology of cholesterol, will be summarized and discussed after the pathological changes have been reviewed, changes about which much has been learnt during the last twenty years. The early work was admirably reviewed by McNee (43) in this Journal in 1914, and will be referred to as briefly as possible here, but in some directions a great deal has been done since then.

*Cholesterol in the Blood in Jaundice and Gall-stones.*

The various pathological conditions cannot be taken in any very logical order till the position is better understood, but it is convenient to take jaundice first. The amount of cholesterol in the blood is increased in all cases of chronic obstructive jaundice, but not in hepatic disease unaccompanied by jaundice, e.g. cirrhosis (43); as the increase is mainly if not entirely in free cholesterol (31), and this is the form in which it is usually excreted in the bile, the retention is probably due to obstruction and is analogous to the retention of bile-salts and pigments. The increase in jaundice is not as great as in the other conditions described, but may be considerable, and in acholuric jaundice, where there is no obstruction but excessive haemolysis, the content of the blood is low.

There is general agreement about the high values found in obstructive jaundice due to gall-stones, but rather divergent results in some other types of jaundice and liver disease. Rothschild and Felson (72) find that in obstructive jaundice due to gall-stones the amount of cholesterol in the blood is much increased, ranging from 0.25 to 0.7 per cent., the lower values occurring in the cases with fever. In cirrhosis the figures are nearly always normal, but in one patient it was high and in two who died soon after it was low. In acute yellow atrophy it is always low, and in cases of carcinoma sometimes low and sometimes high, but generally normal, presumably because of two opposing tendencies, neoplasms producing a decrease and obstructive jaundice an increase in the amount of cholesterol in the blood. In catarrhal jaundice there is generally no change.

In a recent paper the cholesterol and bilirubin content of the blood under various conditions have been compared (154). In obstructive jaundice and some diseases of the liver parenchyma both are retained, but they do not always run parallel, for the cholesterol retention may last for weeks after the bile-pigments have disappeared. In another group of cases (nephritis, arterio-sclerosis, &c.) the cholesterol was found to be retained while the bilirubin was unchanged, and in a third group (heart failure without arterio-sclerosis) the bilirubin might be increased while the cholesterol was normal or subnormal.

It is reasonable to suppose that the retention of cholesterol in obstructive jaundice and in some other liver conditions is a secondary accidental result which throws no more light on the normal functions of cholesterol than of the bile-salts, especially as we are still ignorant of why cholesterol should be excreted in the bile.

Because of the well-known association between pregnancy and the development of gall-stones, Chauffard has urged that the latter are produced partly because of the large amount of cholesterol in the blood and in the bile during pregnancy (111). He claimed further that this high value continued and was useful in diagnosis in cases of gall-stones. This has been confirmed by various workers (45, 112, 133, 135, 147). On the other hand, Denis (55) and Gorham and Myers (63) found no constant increase, and Reimann and Magoun (67) and

Schnabel (77) concluded that it was frequently just as high in other abdominal conditions and was not of much use in diagnosis. The most convincing results are those of Myers (75). The method was carefully controlled and the cases of gall-stones were part of a long series of various pathological conditions. The results in these agreed with what had been found by the digitonin method, and in cases of gall-stones the figures were quite normal.

These discrepancies have been discussed by the present author in this Journal, and his own experimental results give no support to the view that the cholesterol in the blood is raised in cases of gall-stones (148). Since then the subject has again been referred to by Moynihan (159), but in none of those who have found high values for the cholesterol content of the blood in cases of gall-stones is it specifically stated that the patients were not jaundiced at the time of examination.

While the large amount of cholesterol in the blood and in the bile during pregnancy would provide a natural explanation of the known connexion between pregnancy and gall-stones, this can only be one factor, since gall-stones are not known to occur in the other conditions where the amount of cholesterol in the blood is increased. Probably this increase is an important factor in the aetiology, but the evidence is against the increase continuing long enough to be useful in the diagnosis.

#### *Cholesterol in the Blood in Nephritis and Arteriosclerosis.*

Several workers, mostly Russian, have found that in rabbits (but not so far in other animals) changes in the intima of the larger arteries can be induced by feeding them for a long time on a diet rich in cholesterol (42), and the amount in the blood and in the aorta itself is greatly increased in arterio-sclerosis (19). These results have been frequently confirmed and need not be discussed, as little has been added since they were reviewed by McNee (43). Their significance in human pathology is very doubtful, because herbivorous animals are not accustomed to cholesterol in the diet, and similar results have not been obtained in any carnivorous animals. The work of Evans (91) makes it more probable that arterio-sclerosis is generally the result of infection.

The amount of cholesterol in the blood is often increased in cases of nephritis (25, 38, 40), and in eight cases of Klinkert's, though most were of the chronic interstitial type, two at least were diagnosed as parenchymatous. Epstein and Rothschild (59) have emphasized the increase in chronic parenchymatous nephritis, the cholesterol value being very high, up to 1.2 per cent. They do not find a corresponding increase in other types of renal disease, the lipid content being diminished in uraemia with the cholesterol often as low as 0.08 per cent. Henes (74) finds it increased in all cases of chronic nephritis, but agrees that it falls as uraemia develops.

MacAdam and Shiskin (162) have recently shown that a low cholesterol content of the blood is often a useful indication of danger after operations

for enlarged prostate, even in cases where the estimation of the urea in the blood gives no information of value. They attribute this to the poor resistance of these patients to infection spreading up the genito-urinary tract, but it may also be an indication of oncoming uraemia.

In Chauffard's series of cases, where the cholesterol content of the suprarenal was estimated after death, chronic intestinal nephritis, hypertension, and uraemia all figure among the cases where the content was unusually high (149). Kahn (84) found that the cholesterol content of the blood was normal in acute nephritis, and raised in about one-quarter of the cases of chronic interstitial and parenchymatous nephritis, the highest figures being found in the latter disease. According to an early observation of Panzer (7) cholesterol is found in the parenchyma of the kidney in fatty degeneration (large white kidney). In the nephritis produced by poisoning with corrosive sublimate the cholesterol content of the blood is increased, but this does not happen if nephritis is produced by poisoning with uranium, chromic acid, or cantharides (154).

In some experiments by Dewey (51) on feeding rabbits with cholesterol<sup>1</sup> infiltration of the kidney occurred fairly frequently, associated with degeneration of parenchymatous structures, so that the kidney somewhat resembled the large white kidney of human pathology; the liver was infiltrated in most cases, and as this does not usually occur in carnivora it is probably due to the small amount of cholesterol to which the liver of the rabbit is accustomed; but in the spleen there was little deposited. Curiously enough, arterio-sclerotic changes were only produced in one of these rabbits.

These experiments with cholesterol feeding suggest an analogy with the changes in eclampsia. In addition to the well-known clinical resemblances between this and nephritis, the amount of cholesterol and fibrinogen in the blood are both increased. Possibly the raised cholesterol in the blood and the tendency to disorders of the liver and kidney in pregnancy are all due to some metabolic change, similar to that which may be produced in some cases of nephritis.

Nephritis is one of the diseases in which lipaemia is liable to occur, and haemorrhage in patients with nephritis will induce it specially readily. Bloor found that in this lipaemia the total fatty acids in the plasma and the lecithin in the corpuscles shared the greatest increase, and thought that there was retarded fat assimilation owing to the acidosis (62). Linder and his fellow workers found that in nephritic patients with lipaemia there was a greater increase than normal in the fatty acids and lecithin of the plasma after feeding on fat, but that the cholesterol was unchanged, possibly because the observations were not continued for long enough (157). They thought, as the result of their experiments, that

<sup>1</sup> The rabbit is unusual in several particulars, and it is therefore not justifiable to assume that conclusions drawn from the rabbit are applicable to man. It is the only animal in which gall-stones and arterio-sclerosis have been produced by feeding with cholesterol, probably because the rabbit is not accustomed to much cholesterol. It is also exceptional as regards haemolysis (see page 411), and Price Jones has shown that the anaemia following haemorrhage in the rabbit is more like pernicious anaemia than the secondary anaemia of men.

the oxidation of fat was carried out as readily as in health, but that the mechanism which transfers fat from the blood to the tissues was upset. This will be discussed later in connexion with the explanation of the lipaemia which occurs in other pathological conditions.

The views of Epstein about chronic parenchymatous nephritis, and about the relationship of basal metabolism and the cholesterol value of the blood, are of interest. He suggested that this type of nephritis is really a general metabolic disorder associated with hypothyroidism, the nephritis being only part of the picture (60). Du Bois and his fellow workers found the basal metabolism diminished in nephritis with oedema (61), unchanged in other mild types of nephritis, and slightly increased in cases of chronic interstitial nephritis and uncompensated cardiac disease where there was some acidosis (53), but none of the changes were very great.

Epstein's ideas have not met with at all wide acceptance, but from these observations, whether accurate or not, he was led to determine the amount of cholesterol in the blood in thyroid disorders, and found it diminished in exophthalmic goitre and increased in myxoedema, returning to normal as either condition improved (110). If there is any diminution of cholesterol in the blood in Graves's disease, it is probably associated with the increased metabolism involving some disorder of fat metabolism. It might explain the great liability of these patients to infectious diseases (92), as a low cholesterol content in the blood and a poor degree of immunity to infection seem to be associated (see later). Though these conclusions have not been confirmed, they receive some support from the observation that removal of the thyroid in animals (141) is said to be followed by a rise, and the injection of thyroid extract (124) by a fall in the percentage of cholesterol in the blood. As adrenalin is known to raise the basal metabolism (73), these results would agree with the experiments of Joelson and Shorr, who found that removal of the suprarenals was followed by an increase of the cholesterol content of the blood (152).

Although much of this work requires confirmation, there is some evidence associating increased basal metabolism due to overactivity of the thyroid or the suprarenals with a decreased amount of cholesterol in the blood. Obviously other factors must also be important, for there are many exceptions to this attempted generalization, and any connexion between the amount of cholesterol in the blood and changes in the degree of thyroid activity cannot be regarded as firmly established.

Evidently more work is needed to be certain of the exact conditions under which the cholesterol in the blood is increased in nephritis, but there is general agreement that it is likely to be increased in cases of chronic parenchymatous and chronic interstitial nephritis, especially the former, and that it often falls as uraemia develops.



*Cholesterol in the Blood and Lipaemia in Diabetes Mellitus.*

One of the earliest observations on the cholesterol changes in the blood was in diabetes (6); the increase is rather irregular in moderate cases, but may reach very high figures in severe ones, up to more than four times the normal (0.8 per cent. Myers (75)). In Klinkert's cases (40), where he classified the acidosis as slight the average cholesterol figure was 0.29 per cent., where he classified it as severe the figure was 0.40, and in one case where there was no acidosis the figure was within normal limits. It is just in these cases of severe derangement of carbohydrate metabolism with acidosis that lipaemia is most marked, and as there is no other obvious reason why the cholesterol in the blood should be raised in diabetes, it seems most reasonable to associate it with the increased fat metabolism as in pregnancy.

The occurrence of lipaemia in diabetes has been known for a long time, and less commonly it occurs in nephritis and in chronic alcoholism. Of the ten cases indexed in the Guy's Hospital Reports (the first being in 1901), eight were in diabetes mellitus and two in nephritis, one of the latter being fully reported in this Journal by Ryffel (57).

Bloor estimated the total lipid content of the blood in diabetes and found the normal value of 0.5 per cent. sometimes increased nearly ten times (98), and the lecithin and cholesterol also increased as in alimentary lipaemia, the changes taking place in the same order (99). In most cases the free cholesterol in the plasma was increased more than the esters of cholesterol, but in some cases the increases were about the same (54). In his opinion it is the mechanism for the outflow of the lipoids from the blood which is disordered, and the hormone responsible for this is absent in diabetes, but the fat and total lipoids in the blood remain very constant when the fat in the diet of the diabetic is enormously increased (100, 132), and this shows almost conclusively that his explanation is not the correct one. This will be discussed later with the other types of lipaemia.

There is a well-known association of xanthoma with diabetes and jaundice, both conditions in which the amount of cholesterol in the blood is raised. The yellow patches themselves consist of fat and cholesterol, the amount in the blood being also raised (32). The secretion of the sebaceous glands in many animals consists largely of cholesterol, and lanoline obtained from wool fat is one of the purest cholesterol compounds which occur in nature. Walter, after an elaborate investigation into the secretion of the various cutaneous glands in different rodents (151), concludes that in general they secrete considerable quantities of cholesterol and its derivatives. Probably, where the amount in the blood is high, more than usual is excreted through the skin as in the bile, and in susceptible persons xanthoma will result.

In diabetes produced experimentally the cholesterol of the blood is increased, and can be reduced by injections of insulin, though normally this has no effect (142). Artom claims in his experiments on autolysis in the liver that



if the pancreas has previously been removed there is an increased disappearance of cholesterol from the liver, so that it is possible that the change in diabetes consists of the removal of the cholesterol stores of the liver and a decreased storage by other tissues.

This is little more than speculation, but in the clinical significance of cholesterol in diabetes we are on safer ground. Gray (66) and Remond and Rouzaud (122) suggested that the higher the amount of cholesterol in the blood the worse the prognosis. The fullest results are to be found in a recent paper by Gray (150). The total amount of fat was estimated by Bloor's method, i. e. for the total fatty acid and cholesterol, and in many of the cases the cholesterol was also determined separately. Unfortunately lecithin was not estimated.

Taking the changes in the total fat first, it was found to be abnormal in 80 per cent. of these cases, i. e. above 0.67 per cent., which was the highest figure found by Bloor in normals. This means that in diabetes the fat is abnormal nearly as frequently as the sugar in the blood. The increase was not as a rule enormous, and in only 15 per cent. of the cases was it above 1.5 per cent. The longer the duration of the disease, the lower the average amount of fat in the blood, e. g. 1.26 per cent. in cases lasting from 1 to 3 years, and 0.80 in cases lasting from 7 to 20 years. This rather paradoxical result is probably due to the earlier death of patients with a high percentage of fat in the blood, and in fact most long-lived diabetics were found to have less than 1 per cent. of fat in the blood. Conversely, the higher the blood-fat in diabetes, the worse was the prognosis, and Gray gives a table which shows this very clearly.

The amount of cholesterol in the plasma was also found in a smaller number of cases, and this too shows that the larger the amount of cholesterol in the blood the worse the prognosis. The two tables suggest that the cholesterol is a better guide than the total fat. Where the cholesterol was grouped as 'possibly not higher than normal', the average duration of life after the blood examination was over four years. Where it was grouped as 'much raised' (more than one-third of all the cases), the length of life was less than two years.

Another interesting conclusion was that the greater the amount of fat in the body the less the amount in the blood. The highest values were found in patients who were much emaciated, and in general changes in the amount of fat in the blood corresponded to and varied with the amount of sugar. This paper has a special theoretical value, because practically all the results were obtained before the introduction of insulin, and such an opportunity will hardly occur again.

In diabetes the facts about cholesterol are more clearly established than in several other pathological conditions. In all severe cases the amount of fat and cholesterol in the blood is increased, and in these cases, when there is acidosis, lipaemia is also present. Roughly the lipaemia and the amount of cholesterol vary with the severity of the case; both probably depend on the increased metabolism of fat following on the inability to deal with carbohydrate.

*The Decrease of Cholesterol in the Blood in Anaemia and some other Conditions.*

The conditions so far considered have been those in which the amount of cholesterol in the blood is increased. This is diminished in fevers, in the cachexia of cancer, and in anaemia (43, 75), and, as Landau showed, the amount in the suprarenal is much diminished in patients who have died of bacterial and pyogenic infections (36). Chauffard has studied the cholesterol content of the suprarenal in a large number of cases and found it specially low in pulmonary tuberculosis, pneumonia, typhoid, tuberculous meningitis, and septicaemia (149). As the suprarenal content generally varies with the amount present in the blood, all these conditions may be included. In many of these the low value is probably associated with a low degree of immunity in patients who are severely ill (see later). In cancer the cause is not very clear, but it has generally been found in most types of malignant disease, though in cancer of the liver it may sometimes be high owing to the associated jaundice (72); as it is reduced in all types of anaemia, this cause will frequently be operative in cases of malignant disease.

One of the earliest observations on cholesterol and anaemia was that of Erben (4), who found in chlorosis that the cholesterol in the blood was decreased, and subsequently this has been found reduced in all sorts of anaemia. Because of the effect of cholesterol in protecting the red cells against haemolysis by saponin, and because of the low cholesterol value found in pernicious anaemia, it was thought that these two factors were related (78), but the amount of cholesterol in the blood is generally about equally reduced in pernicious, splenic, or simple secondary anaemia (119), and in a series of cases where the value was low in all types, in pernicious anaemia it was often actually higher than the others (72). As the patients recover from the anaemia the amount of cholesterol in the blood increases. This fall in all sorts of anaemia does not depend directly on the decreased corpuscular content, for the plasma content is just as much reduced (119).

These changes are difficult to explain; if anaemia is produced suddenly in the rabbit by the removal of 70 c.c. of blood, or more gradually by the removal of 10 c.c. daily for five days, a visible lipaemia follows, and it is due to an increase of the fat, lecithin, and cholesterol in the blood (Boggs and Morris (16)). This was confirmed by Horiuchi (96), and Bloor found the changes the same as in other lipaemias. The fat in the blood appears without any special amount being present in the diet, and to a greater extent if much fat is added to the diet, and the phenomena are just the same in either case (98). Lipaemia has sometimes been found in patients after severe haemorrhage (102).

Bloor supposes (98) that the anaemia produces a specially large inflow of fat from the tissues to the blood, but does not give any reason for this, and more likely the red corpuscles are generally responsible for producing some change in the lipoids by which they can be removed from the blood to the tissues, and when

these are not enough to produce this change, the lipoids accumulate. In favour of this view, alimentary lipaemia cannot be produced in the rabbit, but in the anaemic rabbit it can be produced easily (46). This, too, will be further discussed in connexion with the other types of lipaemia.

Against this state of affairs in acute anaemia must be set the usual findings that the amount of cholesterol in the blood is low in all types of chronic anaemia. Here, perhaps, some adaptive mechanism has been called into play by which the inflow of lipoids into the blood is diminished, because they cannot be adequately removed.

*Cholesterol and Haemolysis of the Red Cells.*

The influence of cholesterol in inhibiting haemolysis by saponin suggests that these changes of the cholesterol content of the plasma may be of importance in this connexion, especially as injections of saponin increase the cholesterol content of the blood (44). Haemolysis may be produced in many quite different ways, among others by hypotonic saline solutions or by a substance like saponin. The greater the resistance to haemolysis by saponin, the less the resistance to haemolysis by hypotonic saline in all the animals recorded by Bayliss, with the exception of the rabbit (79).

TABLE II. *Haemolysis by Osmosis and by Saponin compared with the Cholesterol Content of the Plasma in Various Conditions.*

Disease.	Resistance to Haemolysis.		Cholesterol Content of Plasma.
	By NaCl.	By Saponin.	
Obstructive jaundice	Increased	Decreased	Much increased
Pernicious anaemia	Slightly increased	Slightly decreased	Decreased
Acholaric jaundice	Greatly decreased	<del>Greatly decreased</del>	Decreased
Splenic anaemia	Slightly increased	Slightly increased	Decreased
After splenectomy	Slightly increased	Slightly increased	Increased
Diabetes, nephritis, and pregnancy	No known change	No known change	Much increased

Similarly, in human obstructive jaundice the resistance of the red cells to haemolysis by saponin is much diminished, but to hypotonic saline it is increased (McNeal (22)); and in pernicious anaemia the same change is found to a lesser degree, resistance to haemolysis by saponin being slightly diminished (22, 39), but to hypotonic saline slightly increased (68). This could be readily explained by a varying distribution of two substances with opposite effects, one inhibiting one type of haemolysis and the other the other.

In splenic anaemia and after splenectomy the resistance is increased against both reagents, and in acholaric jaundice it is greatly diminished against both. In a patient with this disease (101) whom I had the opportunity of re-examining recently, haemolysis was complete with saponin 1 in 33,000, partial with saponin

*Mistake*

*Mistake*

~~1 in 100,000, and very slight with saponin 1 in 330,000; while in the normal control it was complete with saponin 1 in 3,000, partial with saponin 1 in 10,000, and only slight with saponin 1 in 33,000.~~ In Table II the relative resistance against haemolysis is summarized and compared with the cholesterol content in the various conditions to see if the two can be correlated. I have not found any systematic examination of the resistance to haemolysis in diabetes, nephritis, and pregnancy. A few individual cases do not appear to show any change and the subject is being further examined.

From the apparent discordance of these results other factors must be involved, and no satisfying explanation can be hoped for till a considerable advance has been made in our knowledge of the constitution of the cell membrane of the red corpuscles, and of variations in its permeability according to its cholesterol and lecithin content. Probably the most important factor is the ratio of lecithin to cholesterol, an increase in this ratio meaning a decreased osmotic resistance (95). The ratio is about two in the corpuscles and one in the plasma, and it remains constant normally and in many pathological conditions (52), but not in lipaemia. The data for the lecithin content in most of these diseases are not yet available. This mutual effect of lecithin and cholesterol has been investigated recently by Corran and Lewis (146), who find that the optimum ratio for various reactions is between those given for the corpuscles and for the plasma; for example, with this ratio the greatest emulsifying effect is produced on an olive oil and water system, and the oxygen intake is greatest in a system consisting of cholesterol, lecithin, and ferric chloride.

Unlike cholesterol, lecithin inhibits the haemolytic action of bile-salts (12) and has no effect on saponin. Under normal conditions in the body Ponder has shown that the inhibitory effect of the plasma is mainly due to the proteins because of their much greater concentration, but that the cholesterol is also effective in inhibiting haemolysis by saponin, and lecithin in inhibiting haemolysis by bile-salts (134).

There is some evidence that the spleen may be concerned in these changes, for the resistance of the red cells in the splenic vein is less than elsewhere in the body (86, 119), and if blood is taken from the splenic vein immediately after death, when it has stagnated in the organ after some minutes, the resistance is diminished just as much as in acholuric jaundice (118). The change produced by the spleen is only in the surface layer of the corpuscles, for if these are washed with saline their resistance is the same as that of corpuscles from other parts of the body. In three cases of acholuric jaundice and in one of splenic anaemia McAdam and Shiskin found the cholesterol in the blood rose enormously after splenectomy (119), and the reviewer has been able to confirm this in two cases examined recently. This suggests that the spleen can destroy cholesterol, although Abelous, as the result of some rather inconclusive experiments on dogs, thought that the spleen was concerned in its formation (94).

Under normal conditions the spleen seems to remove cholesterol from the blood; it may be needed for the formation of new cells, or, in view of the

close relationship of cholesterol and the cholic acid moiety of the bile-salts and the probability that the latter is synthesized from cholesterol, the spleen may be responsible for initiating this change.

Associated with this removal of cholesterol from the plasma is its removal from the surface layers of the red corpuscles, with a corresponding decrease in their resistance to haemolysis by osmosis. The opposite effect of increased resistance to haemolysis has been found by several observers when the spleen has been removed in man, and has been fully investigated by Pearce in animals (64). The relationship of cholesterol to haemolysis is made rather more complex by the claim that cholesterol oleate is responsible for the haemolytic anaemia due to *Bothriocephalus lata* (11).

Professor Stokes, who has very kindly allowed me to refer to his results, has found that a large amount of cholesterol in the blood protects rabbits from the usual haemolytic effect of intravenous injections of saponin. With gradually increasing doses of saponin, rabbits in which the cholesterol in the blood had been increased by special feeding showed much less anaemia than others which were injected with parallel doses while on ordinary diet. In the animals fed on cholesterol the amount in the blood became very high (0.43 per cent.), while there was no great change in the controls. Moreover, two of the three control rabbits became very anaemic and died as the result of injections of saponin, while all the animals fed on cholesterol survived.

This demonstrates conclusively *in vivo* what was already well known *in vitro*, that cholesterol is of great importance in preventing some types of haemolysis. It is clear that the influence of the spleen on haemolysis depends partly on its power of removing cholesterol from the plasma and from the outer layer of the corpuscles. But there is evidence that from many points of view it is the ratio of lecithin to cholesterol which is of importance, rather than the absolute quantity of the latter, and so far the data about lecithin are not very extensive. Except in acute anaemia, when the cholesterol in the blood is raised owing to the lipaemia, all types of anaemia agree in showing a much decreased cholesterol content of the blood—of the plasma as well as of the corpuscles.

#### *Cholesterol and Sedimentation of the Red Cells.*

During the last few years the rate of sedimentation of the red corpuscles has been widely studied. It is increased in anaemia (105), tuberculosis (82), nephritis (87), and pregnancy (83, 87) among other conditions. The increased rate of sedimentation and the increased amount of cholesterol in the blood ran a parallel course during pregnancy, and Kurten (85) and Linzenmeier (88) have shown that cholesterol and fibrinogen hastened, while lecithin retarded sedimentation. Obviously the increased rate is not only, or even mainly, due to cholesterol, for it is also rapid in anaemia and tuberculosis, where the amount in the blood is diminished.

The whole subject of the rate of sedimentation of the red corpuscles has



been admirably dealt with in a monograph of Fåhræus, which all interested should read (87). The rate is very low in the new-born, considerably faster in women than in men, and enormously faster in women during pregnancy. It is also increased in a very large number of different diseases, sometimes more than, but often not as much as, in pregnancy (87).

The production of the buffy coat in blood removed by venesection depends partly on the rate of coagulation, but mainly on the rate of sedimentation, the latter being increased in many diseases, while the former is generally not much affected. In a fascinating survey of the earlier literature on this subject Fåhræus points out how important was the buffy coat in the production of the older pathological speculations, and incidentally how it formed the main rational basis for blood-letting.

Fåhræus showed that the sedimentation rate increased with the readiness with which the red cells agglutinated and with a diminishing number of cells, the former being the more important. The agglutination referred to is that involved normally in rouleaux formation and depends mainly on the properties of the plasma, being produced slightly by serum albumin, rather more by serum globulin, and much more by fibrinogen. Some experiments on the effect of heat demonstrate clearly that this phenomenon is not at all the same as that produced by the specific agglutinins. In a plasma in which the rate of sedimentation is increased, precipitation with neutral salts such as ammonium sulphate shows that the amount of fibrinogen and the ratio of globulin to albumin are both increased.

Gelatin and cholesterol have a somewhat similar effect to fibrinogen, so that this agglutination, with the secondary result on the rate of sedimentation, seems to be a physico-chemical effect depending on the colloidal condition of the plasma. By some most ingenious experiments Fåhræus has demonstrated that these reactions actually take place in the blood-vessels and are not merely *in vitro* phenomena (87).

The importance of fibrinogen has been confirmed by Gram (105) and Starlinger (103). The former has specially investigated anaemia as an additional factor, and the latter has confirmed the rôle played by agglutination. Working from quite a different point of view, de Wesselow found that the fibrinogen of the plasma was increased in amount both in pregnancy and nephritis (113), and Kollert and Starlinger found that in nephritis with much albuminuria there was an increase of fibrinogen and that the ratio of globulin to albumin was increased (115). The latter change was not confirmed by Kahn (84), but has recently been substantiated by Linder and others (157), who found that the globulin to albumin ratio may rise to two or higher instead of being about one-half, the change depending mainly on the reduced albumin.

This sedimentation test has been widely used in tuberculosis, and is found to give some indication of the severity of the disease and of the reaction to treatment (158). All these factors suggest that in the increased ratio of globulin to albumin, and in the increased amount of fibrinogen in the plasma, colloid



changes are produced which are intimately associated with the reaction of the body to disease.

The ratio of cholesterol to lecithin again seems to be of importance in this connexion, because cholesterol increases the rate of sedimentation and lecithin retards it. But it is not nearly as important as fibrinogen, for the rate of sedimentation is almost as much increased in various conditions where the amount of cholesterol in the plasma is low as in those where it is much increased.

### *Cholesterol and Immunity.*

No attempt has been made here to deal fully with this branch of the subject, and only a few papers are referred to which show the trend of recent work, so as to give some idea of the relationship of this and the other aspects under discussion. There is general agreement that in most acute infections the cholesterol content of the blood and of the suprarenal content is low, especially in those dying of the disease (36, 149). In pneumonia Kipp also has found that it is very low (78).

On the other hand, during recovery and the development of immunity the amount of cholesterol in the blood is said to increase. The injection of diphtheria antitoxin lowers the cholesterol content of the blood, and cholesterol given beforehand increases the protective action against this (124). Beumer confirmed the protective action against diphtheria toxin and found that after cholesterol animals could easily withstand what was previously a lethal dose (125). Barbary (50) found that the mortality of soldiers with septic wounds was diminished after injections of cholesterol, a result which he attributed to their increased immunity. The increase of cholesterol in the suprarenal cortex some time after the injection of this toxin suggests the mechanism of developing immunity (108), and after the injection of vaccines the agglutinating power of the blood and its cholesterol content are said to run parallel (140). In anaphylactic shock the cholesterol content diminishes at once with the fall of blood-pressure, and rises above normal in the following hour (129). Dörle (121) found that after feeding on cholesterol there was a delay in the clotting-time, which appeared after two hours, reached its minimum in five, and disappeared after ten hours.

There are various other aspects of cholesterol which have not been touched on—for example, the part it plays in the production of the Wassermann reaction. Nor has anything been said of the experiments on growth, on diets free from cholesterol and where cholesterol is added to a fat-free diet, because these are probably influenced by the recent work on the important physiological changes produced in cholesterol by ultra-violet light (163, 164), which it is still too early to assess.

### *Summary and Discussion.*

The known physiological facts may be summarized first. Cholesterol occurs in every cell generally associated with lecithin and is necessary for life. With

the other lipoids it is essential in the structure of protoplasm, for the percentage in various tissues is characteristic and tends to remain constant. Cholesterol and lecithin are of special importance in the cell membrane and many of its functions depend on their physico-chemical properties. Possibly they collect at the surface of the cell owing to these properties. The part cholesterol plays in immunity probably depends on its function in the cell membrane, rather than on any specific chemical properties, but this aspect of the subject is only briefly referred to here.

About half the cholesterol taken in the food is absorbed and appears in the blood as free cholesterol. It is excreted in the bile, but a portion of this is reabsorbed. Although there is evidence that the body is able to synthesize cholesterol, every attempt is made to conserve its supplies. In addition to its other functions, cholesterol is probably of importance for the synthesis of bile-salts. Its function in the bile is unknown, but its reabsorption suggests that, like the bile-salts, it is of some help in fat absorption.

When feeding on fat is long continued there is a definite train of events known as alimentary lipaemia. The fat increases first, then the lecithin, and finally the cholesterol. Continued feeding on cholesterol produces a very similar result. Lecithin is synthesized from fat, and probably the red corpuscles play an important part in this and turn a large proportion of the fat into lecithin. It may be that cholesterol is also a stage in fat metabolism and is synthesized in the same way, and there is some evidence that this can happen; or it may be that the cholesterol is increased because it is essential to keep the ratio of cholesterol to lecithin constant. The former would provide the most natural explanation of many of the variations in disease, but it may seem a very unlikely suggestion and the phenomena of haemolysis show that this ratio is very important. The main argument against this second explanation is that in lipaemia the cholesterol is increased more than the lecithin, so that at present the first explanation seems the more probable.

In starvation there is a somewhat similar series of events, and the amount of cholesterol in the blood is increased, probably because the body is living on its own tissues, which contain a high proportion of fat and cholesterol. The ratio of cholesterol to fatty acids in various tissues is also increased, and this makes them capable of imbibing more water.

From about the fourth month of pregnancy the cholesterol content of the blood continues to rise, and this lasts for some time after child-birth. Here again there is a great increase in fat metabolism, first for the growth of the child and later for the production of milk of which the cholesterol content is high, to make up for the small amount in the child's blood. The milk fat is synthesized from phospho-lipins (probably lecithin) circulating in the blood. In pregnancy, as in other conditions where the cholesterol in the blood is increased, more than usual is excreted in the bile.

It has been suggested that the suprarenal is the gland responsible for the production of cholesterol, but the facts can be equally well explained by suppos-

ing that the suprarenal changes follow those in the blood. It is uncertain where cholesterol is produced or destroyed, but there is some evidence that it is produced by the liver and removed from the blood by the spleen.

In disease the main facts which require explanation are the decreased amount of cholesterol in the blood in anaemia, in many acute infections, and in malignant disease; and the increased amount in jaundice of the obstructive type, in severe diabetes associated with acidosis, and in many cases of chronic nephritis both of the interstitial and parenchymatous types.

As regards the former group there is little physiological evidence, for nothing is known about the cholesterol content of the blood being decreased except in disease. In the acute infections it seems likely that it is associated with poor resistance to the disease and that as immunity increases the amount of cholesterol in the blood rises. It is in the more advanced cases of malignant disease that the cholesterol content is so frequently low, and often in these cases the associated anaemia may be partly responsible. A low value suggests a gloomy prognosis, especially as in nephritis, where it is generally high, it falls as uraemia develops, but in diabetes, where the amount is raised, a high value is equally serious. Were it not for the low values found for long periods in anaemia, one would say that any great diminution in the cholesterol content of the blood lasting for more than a short time was not compatible with life.

Anaemia stands alone in one other particular, for while the cholesterol in the blood is decreased in all forms of chronic anaemia, it is raised in acutely produced anaemia when it is associated with lipaemia. The red cells are concerned in the production of lecithin from fat, and possibly they may play some more general part in the removal of all the lipoids from the blood, or in their utilization for the general purposes of this body.

Animals are frequently bled to encourage fattening, and the decreased red cells may lead first to an increasing concentration of lipoids in the blood, and then to their storage in the body instead of their utilization. If this be so, one must suppose that in chronic anaemia the body has reacted by diverting metabolism along other lines, and that cholesterol no longer appears in the blood because the metabolic changes of the lipid group have been reduced to a minimum. Bloor supposes that the changes in acute anaemia are due to the blood being flooded with lipoids from the tissues, but there is no obvious reason why this should be so. Certainly the phenomena are just the same when the lipaemia is produced by fat-feeding, but the evidence shows that it occurs on a quite normal diet and probably depends more on the inability of the blood to deal with the normal amount of fat owing to the smaller number of red cells. The cholesterol might, as Bloor suggests, be increased to keep the ratio of cholesterol to lecithin constant, but actually the former increases more than the latter in lipaemia. It is difficult to explain this if the cholesterol is only increased to balance the lecithin, but easier to understand if cholesterol is also a stage in fat metabolism.

In some of the conditions in which the amount of cholesterol in the blood is

increased we are on more certain ground. In jaundice it apparently depends on obstruction to the normal output in the bile, and it is only where this is interfered with that cholesterol accumulates in the blood, and any effects produced are secondary. Jaundice is also in a different position because the increased cholesterol in the blood does not seem to be associated with any of the other changes to be discussed.

In all cases of severe diabetes with acidosis the amount of cholesterol in the blood is increased, and this is sufficiently constant to be a reliable guide to prognosis. It seems reasonable to compare this with the conditions found in starvation, in which there is an increase of fat metabolism owing to the absence of carbohydrate metabolism. Bloor suggests that there is abnormally slow output of fat from the blood owing to the absence of some hormone, but this is very unlikely because when a diabetic is given more fat the lipoids in the blood are not much higher than before. The increased fat metabolism, owing to the difficulty of dealing with carbohydrates, is an adequate explanation, and brings it into line with the conditions in starvation and excessive fat feeding. The frequent association of these two may seem paradoxical, but in both the fat metabolism is increased.

Further justification for attempting to explain all these types of lipaemia on similar lines is the general similarity which was found by Bloor between the lipaemia of alimentary origin and those following haemorrhage, diabetes, and nephritis. Also alimentary lipaemia can be induced more readily in an anaemic animal, and the lipaemia following haemorrhage occurs more readily in a patient with nephritis.

It is very difficult to explain the lipaemia and increased amount of cholesterol in the blood in nephritis. Cholesterol is certainly not a retention product as it is in jaundice, and there is no definite evidence of any important change in metabolism. There are two changes which tend to occur in the blood in nephritis which may have some bearing on this part, the acidosis and the increase in the amount of fibrinogen and in the ratio of globulin to albumin. The latter changes also occur in pregnancy, but they occur as well in most acute infectious conditions when the amount of cholesterol in the blood is low; the former may be of importance.

Bloor supposed that in nephritis fat assimilation was retarded owing to the acidosis, and Linder and van Slyke concluded that oxidation was carried out as readily as usual, but that the mechanism transferring fat from the blood to the tissues was upset. If nephritis is looked on as a disease of the kidney only, it is difficult to see how these changes are brought about, unless the induced acidosis has some effect on fat metabolism, and of this there is no evidence at present.

The increased cholesterol in the blood is closely associated with lipaemia. Apart from jaundice, six conditions have been described in which it may occur. In four of these lipaemia is likely to occur, and in four there is a tendency to acidosis. In acute anaemia, and after fat ingestion, the increase in cholesterol is often associated with lipaemia, in pregnancy and starvation with acidosis, and in

nephritis and diabetes with lipaemia and acidosis. What is the real connexion between acidosis and the other two conditions must at present be left unexplained. The connexion of cholesterol and lipaemia has been dealt with fully.

Two other aspects of the question have been touched on shortly—the influence of cholesterol on haemolysis and on sedimentation of the red cells. For the former the ratio of lecithin to cholesterol is of importance, and an attempt to maintain this ratio constant may be partly responsible for many of the changes described.

The rate of sedimentation of the red cells is also diminished by any increase in the ratio of lecithin to cholesterol, suggesting some analogy with the points already discussed. But much more important in this connexion is an increase in the amount of fibrinogen or in the ratio of globulin to albumin—changes which are certainly found in nephritis and to some extent at any rate in pregnancy and various infective conditions. It seems as though these two factors require investigation in connexion with the lecithin to cholesterol ratio in a large number of diseased conditions.

If this discussion seems to have led to the consideration of certain chemical balances in the blood rather than to any useful clinical generalizations, the writer can only plead that from each point of approach he has been led back to these fundamental points, which suggests that their elucidation might be of great importance in understanding these various diseases.

The writer wishes to thank Professor Laidlaw and Professor Ramsden for their criticisms and suggestions, though they cannot be held in any way responsible for the views put forward.

# REFERENCES.

1. Flint, *Amer. Journ. of Med. Sci.*, Philad., 1862, N.S. xlv.; and Picot, *Journ. de l'Anatome*, Paris, 1872, quoted by Dorée and Gardner (13).
2. Cohnstein, W., and Michaelis, H., *Pflüger's Archiv f. d. ges. Physiol.*, Bonn, 1898, viii. 246, lxix. 76.
3. Ransom, *Deutsch. med. Woch.*, Leipz., 1901, xxvii. 194.
4. Erben, F., *Zeitsch. f. klin. Med.*, Berlin, 1902, xlvii. 302.
5. Bunge, G., *Physiol. and Path. Chem.*, 4th edit., 1902, 81.
6. Fischer, *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1903, clxxii. 218.
7. Panzer, *Zeitsch. f. physiol. Chem.*, Strassb., 1906, xlviii. 519.
8. Pflüger, H., *Biochem. Zeitsch.*, Berlin, 1906, i. 413.
9. Aschoff, L., *Verh. Deutsch. path. Gesellsch.*, Jena, 1907, x. 166.
10. Craven Moore, *Medical Chronicle*, Manchester, 1907, xlvii. 204.
11. Faust, E., and Tallquist, G. W., *Arch. f. exper. Path. u. Pharmacol.*, Leipz., 1907, lvii. 367.
12. Bayer, *Biochem. Zeitsch.*, Berlin, 1907, v. 368.
13. Dorée, C., and Gardner, J. A., *Proc. Roy. Soc.*, Lond., 1908, lxxi. B. 212 and 227.
14. Dorée, C., and Gardner, J. A., *ibid.*, Lond., 1909, lxxxi. B. 109.
15. Windaus, A., *Ber. der Deutsch. chem. Gesellsch.*, 1909, xlii. i. 238.
16. Boggs, T. R., and Morris, R. S., *Journ. of Exp. Med.*, N. York, 1909, xi. 553.
17. Ellis, G. W., and Gardner, J. A., *Proc. Roy. Soc.*, Lond., 1909, lxxxi. B. 129 and 505.



18. Fraser, M. T., and Gardner, J. A., *Proc. Roy. Soc., Lond.*, 1909, lxxxi. 230, and 1910, lxxxii. 559. B.
19. Windaus, A., *Zeitsch. f. physiol. Chem.*, Strassb., 1910, lxvii. 174.
20. Grigaut, A., *Comptes rendus Soc. de Biol.*, Paris, 1910, lxviii. 791.
21. Ellis, G. W., and Gardner, J. A., *Proc. Roy. Soc., Lond.*, 1911, lxxxiv. 461, and 1912, lxxxv. 385. B.
22. McNeal, C., *Journ. of Path. and Bact.*, Camb., 1911, xv. 60.
23. Hermann and Neumann, *Wiener klin. Woch.*, 1911, xxiv. 411, and 1912, xxv. 1557.
24. Albrecht and Weltmann, *ibid.*, 1911, xxiv. 483.
25. Chauffard, A., Laroche, G., and Grigaut, A., *L'Obstétrique*, Paris, 1911, iv. 481.
26. Grigaut, A., *Comptes rendus Soc. de Biol.*, Paris, 1911, lxx. 317.
27. Widal, Weil, and Laudet, *ibid.*, Paris, 1913, lxxiv. 882.
28. Ellis, G. W., and Gardner, J. A., *Proc. Roy. Soc., Lond.*, 1912, lxxxvi. 13. B.
29. Wieland, H., and Weil, F. J., *Zeitsch. f. physiol. Chem.*, Strassb., 1912, lxxx. 287.
30. Chauffard, A., Laroche, G., and Grigaut, A., *Arch. d'Obstér. et de Gyn.*, Paris, 1912, xvii. 401.
31. Widal, Weil, and Laudet, *Semaine médicale*, Paris, 1912, xxxii. 529.
32. Apert, Pechery, and Rouillard, *Comptes rendus Soc. de Biol.*, Paris, 1912, lxxii. 822.
33. Iscovesco, H., *ibid.*, Paris, 1912, lxxii. 920.
34. Gardner, J. A., and Lander, P. E., *Proc. Roy. Soc., Lond.*, 1913-14, lxxxvii. 229. B.
35. Gardner, J. A., and Lander, P. E., *Biochem. Journ.*, Camb., 1913, vii. 577.
36. Landau, *Deutsch. med. Woch.*, Leipz., 1913, xxxix. 546.
37. Mayer, A., and Schaeffer, G., *Journ. de Physiol. et de Path.*, Paris, 1913, xv. 696, and 1914, xvi. 930.
38. Weil, A., and Laudet, M., *Comptes rendus Soc. de Biol.*, Paris, 1913, lxxiv. 882.
39. Bigland, *Quart. Journ. of Med.*, Oxford, 1913-14, vii. 380.
40. Klinkert, D., *Berlin. klin. Woch.*, 1913, l. 820.
41. Bacmeister and Henes, *Deutsch. med. Woch.*, Leipz., 1913, xxxix. 544.
42. Ignatowski (1908), Stuckey (1910), and Anitschkow and Chalatow (1913), quoted by McNee (43).
43. McNee, J. W., *Quart. Journ. of Med.*, Oxford, 1913-14, vii. 221.
44. Porak, R., and Quinquaud, A., *Comptes rendus Soc. de Biol.*, Paris, 1914, lxxvii. 368.
45. Henes, *Journ. of Amer. Med. Ass.*, Chicago, 1914, lxiii. 146.
46. Sakai, S., *Biochem. Zeitsch.*, Berlin, 1914, lxii. 387.
47. Terroine, E. F., *Journ. de Physiol. et de Path.*, Paris, 1914-15, xvi. 386.
48. Bloor, W. R., *Journ. Biol. Chem.*, Baltimore, 1915, xxiii. 323.
49. Rothschild, *Beiträge z. path. Anat. u. z. allg. Path.*, Jena, 1915, lx. 227.
50. Barbary, F., *Bull. de l'Acad. de Méd.*, Paris, 1916, 3<sup>e</sup> sér., lxxvi. 221.
51. Dewey, K., *Arch. Int. Med.*, Chicago, 1916, xvii. 784.
52. Bloor, W. R., *Journ. Biol. Chem.*, Baltimore, 1916, xxiv. 227 and 459, and xxv. 577 and 596.
53. Peabody, F. W., Meyer, A. L., and Du Bois, E., *Arch. Int. Med.*, Chicago, 1916, xvii. 981.
54. Bloor, W. R., and Knudson, A., *Journ. Biol. Chem.*, Baltimore, 1916, xxvii. 107, and xxix. 7.
55. Denis, *ibid.*, Baltimore, 1916, xxiv. 229, and 1917, xxix. 93.
56. Porter, A. E., *Biochem. Journ.*, Camb., 1916, x. 523.
57. Ryffel, J. H., *Quart. Journ. of Med.*, Oxford, 1915-16, ix. 91.
58. Clark, E. R., and Clark, E. L., *Amer. Journ. of Anat.*, Philad., 1917, xxi. 421.
59. Epstein, A. A., and Rothschild, M. A., *Amer. Journ. of Physiol.*, Baltimore, 1917, xlii. 587.
60. Epstein, A. A., *Journ. Amer. Med. Ass.*, Chicago, 1917, lxix. 444.
61. Aub, J. C., and Du Bois, E., *Arch. Int. Med.*, Chicago, 1917, xix. 865.
62. Bloor, W. R., *Amer. Journ. Physiol.*, Baltimore, 1917, xlii. 586, and *Journ. Biol. Chem.*, Baltimore, 1917, xxxi. 575.
63. Gorham and Myers, *Arch. Int. Med.*, Chicago, 1917, xx. 599.



64. Pearce, Frazier, and Krumbhaar, *The Spleen and Anaemia*, Philad. and Lond., 1917.
65. Langmuir, I., *Journ. Amer. Chem. Soc.*, 1917, xxxix. ii. 1868.
66. Gray, H., *Boston Med. and Surg. Journ.*, 1918, clxxviii. 16.
67. Reimann, S. P., and Magoun, J. A. H., *Surg. Gynecol. and Obstet.*, Chicago, 1918, xxvi. 282.
68. Giffen, H. Z., and Sanford, A. H., *Collected Papers, Mayo Clinic*, 1918, x. 102.
69. Myers and Wardell, *Journ. Biol. Chem.*, Baltimore, 1918, xxxvi. 147.
70. Luden, G., *Journ. Lab. and Clin. Med.*, St. Louis, 1917-18, iii. 141.
71. Hueck, W., and Wacker, L., *Biochem. Zeitsch.*, Berlin, 1919, c. 84.
72. Rothschild, M. A., and Felson, J., *Arch. Int. Med.*, Chicago, 1919, xxiv. 520.
73. Sandiford, I., *Amer. Journ. of Physiol.*, Baltimore, 1920, li. 407.
74. Henes, *Arch. Int. Med.*, Chicago, 1920, xxv. 411.
75. Myers, V. C., *Journ. Lab. and Clin. Med.*, St. Louis, 1919-20, v. 776.
76. Knudson, A., *Journ. Biol. Chem.*, Baltimore, 1920, xli, 'Proc.' lxvii.
77. Schnabel, T. G., *Amer. Journ. Med. Science*, Philad., 1920, N. S., clx. 423.
78. Kipp, H. A., *Journ. Biol. Chem.*, Baltimore, 1920, xliii. 413, and xliv. 215.
79. Bayliss, W. M., *Principles of Gen. Physiol.*, 3rd edition, Lond., 1920, 133.
80. Richter-Quittner, M., *Wien. Arch. Inn. Med.*, 1920, i. 425.
81. Windaus, A., and Neukirchen, *Ber. der Deutsch. chem. Gesellsch.*, 1919, lii. 1915.
82. Westergren, A., *Acta Med. Scand.*, Stockholm, 1921, liv. 247.
83. Linzenmeier, *Zentralblatt f. Gynäk.*, Leipz., 1920, xlv. 816.
84. Kahn, M., *Arch. Int. Med.*, Chicago, 1920, xxv. 193.
85. Kurten, H., *Pflüger's Archiv f. d. ges. Physiol.*, Berlin, 1920, clxxxv. 248.
86. Eppinger, *Die hepatolienalen Erkrankungen*, 1920, quoted by Bolt and Heeres (118).
87. Fähræus, R., *Acta Med. Scand.*, Stockholm, 1921, lv. 1-228.
88. Linzenmeier, G., *Pflüger's Archiv f. d. ges. Physiol.*, Berlin, 1921, clxxxvi. 272.
89. Lifschütz, I., *Zeitsch. f. physiol. Chem.*, Berlin, 1921, cxvii. 212.
90. Adam, N. K., *Proc. Roy. Soc.*, Lond., 1921, xcix. 336; 1922, ci. 452 and 516; and 1923, ciii. 676. A.
91. Evans, G., *Quart. Journ. Med.*, Oxford, 1920-21, xiv. 216.
92. Campbell, J. M. H., *ibid.*, Oxford, 1921-22, xv. 55.
93. Krontovsky, A., quoted in *Physiological Abstracts*, Lond., 1920-21, v. 53.
94. Abelous, J. E., *Arch. intern. de Physiol.*, Liège, 1921, xviii. 42.
95. Brinkmann, R., and van Dam, F. E., *Biochem. Zeitsch.*, Berlin, 1920, cviii.
96. Horiuchi, Y., *Journ. Biol. Chem.*, Baltimore, 1920, xlv. 347.
97. Bloor, W. R., *ibid.*, Baltimore, 1921, xlv. 186.
98. Bloor, W. R., *ibid.*, Baltimore, 1921, xlix. 201.
99. Various authors quoted by Bloor (98).
100. Blatherwick, N. R., *Journ. Biol. Chem.*, Baltimore, 1921, xlix. 193.
101. Campbell, J. M. H., *Guy's Hospital Reports*, Lond., 1921, lxxi. 276.
102. Feigl, J., *Biochem. Zeitsch.*, Berlin, 1921, cxv. 63.
103. Starlinger, W., *ibid.*, Berlin, 1921, cxiv. 129.
104. Lemeland, P., *Bull. de la Soc. chim. biol.*, Paris, 1921, ii. 134.
105. Gram, H. C., *Arch. Int. Med.*, Chicago, 1921, xxviii. 312.
106. Gardner, J. A., and Fox, F. W., *Proc. Roy. Soc.*, Lond., 1921, xcii. 358. B.
107. Gardner, J. A., and Williams, S. M., *Biochem. Journ.*, Camb., 1921, xv. 251, 363, and 376.
108. Clevers and Goormaghtigh, *Bull. Acad. Roy. Méd.*, Belgique, 1922, 5 sér., ii. 425.
109. Fox, F. W., and Gardner, J. A., *Proc. Roy. Soc.*, Lond., 1922, xciii. 486. B.
110. Epstein, A. A., and Lande, H., *Arch. Int. Med.*, Chicago, 1922, xxx. 563.
111. Chauffard, A., *La Lithiase biliaire*, Paris, 1922, 43.
112. Flandin, quoted by Chauffard (111).
113. de Wesselow, L. V., *Journ. of Obstetrics and Gynaecology*, Manchester, 1922, xxix. 42.
114. Okuneff, N., *Beiträge z. path. Anat. u. z. allg. Path.*, Jena, 1922, lxxi. 99.
115. Kollert, V., and Starlinger, W., *Zeitsch. f. d. ges. exper. Med.*, Berlin, 1922, xxx. 293.
116. Bloor, W. R., *Physiological Reviews*, Baltimore, 1922, ii. 92.

117. Schafer, E. A., quoted by Bloor (116).
118. Bolt, N. A., and Heeres, P. A., *Biochem. Journ.*, Camb., 1922, xvi. 754.
119. MacAdam, W., and Shiskin, C., *Quart. Journ. of Med.*, Oxford, 1922-23, xvi. 193.
120. Marine and Bannerman, *Amer. Journ. of Physiol.*, Baltimore, 1922, 59.
121. Dörle, M., *Zeitsch. f. d. ges. exper. Med.*, Berlin, 1923, xxxiv. 101.
122. Remond and Rouzaud, *Bull. de l'Acad. de Méd.*, Paris, 1923, 3<sup>e</sup> sér., lxxxix. 60.
123. Wilstätter, R., *Zeitsch. f. physiol. Chem.*, Berlin, 1923, cxxx. 281.
124. Leupold, E., and Sersser, F., *Arch. f. Gynäkol.*, Berlin, 1923, cxix. 552.
125. Beumer, H., *Zeitsch. f. Kinderheilk.*, Berlin, 1923, xxxv. 298.
126. Präbram, *Arch. f. Gynäkol.*, Berlin, 1923, cxx. 90.
127. Asada, K., *Biochem. Zeitsch.*, Berlin, 1923, cxli. 166.
128. Artom, C., *Arch. intern. Physiol.*, Liège, 1923, xxii. 17, 32, and 173.
129. Clevers, M., *Comptes rendus Soc. de Biol.*, Paris, 1923, ii. 965.
130. Fox, F. W., and Gardner, J. A., *Biochem. Journ.*, Camb., 1923, xvii. 94.
131. Meigs, E. B., *Physiological Reviews*, Baltimore, 1922, ii. 215.
132. Marsh, P. H., and Waller, H. G., *Arch. Int. Med.*, Chicago, 1923, xxxi. 63.
133. Rothschild and Rosenthal, quoted by J. J. R. MacLeod, *Physiology and Biochemistry in Modern Medicine* (4th edition), Lond., 1923, 568.
134. Ponder, E., *Proc. Roy. Soc.*, Lond., 1923-24, xcv. 60. B.
135. Bell, J. R., *Brit. Med. Journ.*, Lond., 1924, i. 35.
136. Rous, P., McMaster, P. D., and Drury, D. R., *Journ. Exper. Med.*, N. York, 1924, xxxix. 77.
137. Fox, F. W., and Gardner, J. A., *Proc. Roy. Soc.*, Lond., 1925, xcvi. 76. B.
138. Gardner, J. A., and Fox, F. W., *Biochem. Journ.*, Camb., 1924, xviii. 127, 1058.
139. Robinson, M. E., *ibid.*, Camb., 1924, xviii. 255.
140. Danyasz-Michel and Laskownicki, *Comptes rendus Soc. de Biol.*, Paris, 1924, xci. 632.
141. Rémond, A., and Columbiès, H., *ibid.*, Paris, 1924, xci. 445.
142. Nitescu, C., Inotesti, and Cadariu, *ibid.*, Paris, 1924, xc. 538 and 1067.
143. Heilig, R., and Lederer, K., *Klin. Woch.*, Berlin, 1924, iii. 1765.
144. McMaster, P. D., *Journ. Exp. Med.*, Baltimore, 1924, xl. 25.
145. Leiboff, S. L., *Journ. Biol. Chem.*, Baltimore, 1924, lxi. 177.
146. Corran, J. W., and Lewis, W. C. M., *Biochem. Journ.*, Camb., 1924, xviii. 1358.
147. Wilensky, A. O., and Rothschild, M. A., *Amer. Journ. Med. Sci.*, Philad., 1924, clxviii. 66.
148. Campbell, J. M. H., *Quart. Journ. Med.*, Oxford, 1924-25, xviii. 123.
149. Chauffard, quoted by E. Sharpey Schafer, *Endocrine Organs*, Lond., 1924, 109.
150. Gray, H., *Amer. Journ. Med. Sci.*, Philad., 1924, clxviii. 35.
151. Walter, A., *Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1924, lxxiii. 142.
152. Joelson, J. J., and Shorr, E., *Arch. Int. Med.*, Chicago, 1924, xxxiv. 841.
153. Steinitz, *Zeitsch. f. d. ges. exper. Med.*, Berlin, 1925, xlv. 757.
154. Wichert, M., and Russajewa-Oparina, H., *Zeitsch. f. klin. Med.*, Berlin, 1924, ci. 185.
155. Sandiford, I., and Wheeler, T., *Journ. Biol. Chem.*, Baltimore, 1924, lxii. 324.
156. Iwantscheff, J., *Zeitsch. f. klin. Med.*, Berlin, 1924, ci. 85.
157. Linder, G. C., Lundsgaard, C., and van Slyke, D. D., *Journ. Exper. Med.*, N. York, 1924, xxxix. 930.
158. Michels, G., *Internat. Zentralbl. f. d. ges. Tuberk.*, Würzburg, 1924, xxiii. 241.
159. Moynihan, Sir Berkeley, *Brit. Med. Journ.*, Lond., 1925, i. 393.
160. Shiskin, C., quoted by Moynihan (159).
161. Leathes, J. B., *Lancet*, Lond., 1925, i. 803, 854, 957, and 1019.
162. MacAdam, W., and Shiskin, C., *Brit. Journ. of Surgery*, Bristol, 1925, xii. 436.
163. Rosenheim, O., and Webster, T. A., *Lancet*, Lond., 1925, i. 1025.
164. Hess, A. F., Weinstock, M., and Helman, F. D., *Journ. Biol. Chem.*, Baltimore, 1925, lxiii. 297 and 305.

# PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

## EIGHTEENTH ANNUAL GENERAL MEETING

THE EIGHTEENTH ANNUAL GENERAL MEETING was held on Friday, June 26, 1924, in the Department of Physiology of the University of Bristol, at 10 a.m.

The Secretary read a letter from the President, Sir Byrom Bramwell, expressing great regret for his inability to be present at the meeting. In the absence of the President, the Treasurer, Sir William Hale-White, took the chair.

The minutes of the last General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

*Election of President.* Dr. George Parker was elected President, and on his election took the chair and proposed a vote of thanks to Sir Byrom Bramwell for his services during the year 1923-4.

*Election of Honorary Member.* Sir Byrom Bramwell, the retiring President, was elected an honorary member of the Association.

The election of Officers, members of the Executive Committee, and new members followed.

*Treasurer.* Sir William Hale-White.

*Secretary.* Dr. H. Morley Fletcher.

### *Members for England :*

Professor J. Hill Abram.  
Lord Dawson.  
Professor F. R. Fraser.  
Professor W. E. Hume.  
Dr. J. A. Nixon.  
Dr. H. L. Tidy.

### *Members for Scotland :*

Dr. J. B. M. Anderson.  
Dr. Edwin Bramwell.  
Dr. J. Mackie Whyte.

### *Members for Ireland :*

Dr. W. Boxwell.  
Dr. G. E. Nesbitt.  
Professor W. W. D. Thomson.

### *New Members.*

John J. CONYBEARE, M.D., Medical Registrar and Astley Cooper Student, Guy's Hospital.

A. Hope GOSSE, M.D., Assist. Phys., St. Mary's Hospital.

G. Secretan HAYNES, M.D., Assist. Phys., Addenbrooke's Hospital, Cambridge.

## ASSOCIATION OF PHYSICIANS

- H. Wallace JONES, M.D., Assist. Phys., Liverpool Royal Infirmary.  
D. Murray LYON, M.D., Assist. Phys., Royal Infirmary, Edinburgh.  
John C. MATTHEWS, M.D., Assist. Phys., Liverpool Royal Infirmary.  
Thomas H. OLIVER, M.D., Assist. Phys., Royal Infirmary, Manchester.  
S. Wentworth PATTERSON, M.D., D.Sc., Assist. Phys., Duff House, Ruthin.  
Rudolph A. PETERS, M.D., Whitley Professor of Biochemistry, University of Oxford.  
R. A. ROWLANDS, M.D., Assist. Phys., London Hospital.  
Victor M. SYNGE, M.D., Physician, Royal City of Dublin Hospital.  
F. M. R. WALSH, M.D., Assist. Phys., National Hospital Paral. and Epilep., London.

The Treasurer, Sir William Hale-White, presented his balance-sheet, which showed a balance of £202. The report was adopted.

*Alteration of Rule 2.* Sir Humphry Rolleston had given notice that he would move that Rule 2 be altered to make it possible to elect Foreign Honorary Members, not exceeding five in number. In the unavoidable absence of Sir Humphry Rolleston, the Secretary moved, and Professor Wardrop Griffith seconded the motion, which was carried unanimously. It was agreed that the Executive Committee be requested to draw up a list of eminent foreign physicians for selection at the next Annual Meeting.

*Annual General Meeting in 1925.* It was resolved to hold this meeting in London on the Friday and Saturday before Whitsuntide.

*N.B.—Notice of Motion.* Professor G. R. Murray gave notice that at the next Annual Meeting he would move that in Rule 20 the word *four* be altered to *three*.

## SCIENTIFIC BUSINESS

### FRIDAY, JUNE 6, 10.30 a.m. MORNING SESSION

1. Dr. W. E. Foggie on *suprarenal haemorrhage and its clinical syndrome*. He described the clinical syndromes which might accompany suprarenal haemorrhage. There were three main types:

- (1) In early infancy associated with purpura.
- (2) Before, at, or just after birth.
- (3) As a sequel or in association with other conditions.

One example of each type was detailed.

Dr. Michael Foster referred to cases of suprarenal haemorrhage in cerebro-spinal fever.

Dr. Laugdon Brown and Dr. Veale also spoke.

2. Dr. W. T. Ritchie on *progressive lipodystrophy*. He related three cases in adult women 24, 24, and 38 respectively. In the third case the lipodystrophic process affected the thighs as well as the arms and thorax. No fresh information as to the cause was offered.

Dr. Parkes Weber pointed out that the disease is not always progressive. He advanced the view that the condition is not due to an atrophy of the fat, but to a loss of power on the part of the fat-cells to store fat. He suggested that it might be explained as a redistribution of fat somewhat analogous to the redistribution of pigment in the skin in cases of vitiligo. The fat-cells in the upper part of the body did not atrophy but simply refused to store fat (glycerin-ester), just as the cells in the white areas of the skin in vitiligo refused to hold their normal cutaneous pigment. Some disturbance in the vegetative nervous system might be at the root of the abnormal condition in both cases.

## OF GREAT BRITAIN AND IRELAND

Dr. Poynton asked whether circulatory disturbances were found in any of the cases.

Professor Murray asked if the loss of fat ever began in the lower part of the body and spread upwards, and whether microscopical changes had been found in the underlying muscles.

Dr. Hurst referred to the one-sided loss of fat in hemiatrophy of the face.

Several other members joined in the discussion.

In reply, Dr. Ritchie stated that he was inclined to accept Dr. Weber's suggestion as to the cause of the loss of fat. He pointed out that lipodystrophy might follow a severe shock.

3. Dr. H. W. Barber on *Boeck's sarcoid—benign lymphogranuloma of Schaumann*. Schaumann had shown that lupus pernio and Boeck's sarcoid were probably identical conditions, and his original view was that they were not of tuberculous origin. Later he concluded that these conditions were due to a chronic infection with bovine tuberculosis. None of Dr. Barber's three cases of Boeck's sarcoid showed clinical evidence of tuberculosis: two gave a completely negative complement-fixation reaction, and one a strongly positive result. One of the cases had iritis, as had also two cases recorded by Savatard.

Dr. Parkes Weber asked if Dr. Barber's cases showed giant cells in the nodules.

Dr. Barber, in reply, stated that nodules were found in the spleen, and giant cells were present.

4. Dr. A. F. Hurst on *achalasia of the cardia and other sphincters*. He related a recent case which supported his views on the conditions previously ascribed to spasm of the cardiac end of the oesophagus. The obstruction in these cases was due to an inability of the cardia to relax, and not to spasm. Peristalsis could be observed to take place normally as far as the cardia, and there to stop, owing to a failure of relaxation. In nine cases, all but one were cured by the passage of a thick rubber tube filled with mercury. He suggested that achalasia might explain 'water-brash' and the bringing up of large quantities of clear alkaline fluid. He considered that some cases of pyloric obstruction regarded as pyloric spasm might be also due to a failure of the pyloric sphincter to relax. Ileo-caecal stasis and Hirschsprung's disease might be explained in the same way.

Many members discussed this communication. Dr. Poulton advocated the use of Plummer's bag for dilating the cardia instead of the mercury tube.

Professor Murray referred to Langley's observations on the action of adrenalin in bringing about relaxation of non-striated muscle. He (Murray) had given adrenalin before meals in such cases with good results.

Professor Wardrop Griffith stated that many years ago Sir H. Rolleston had suggested that the cause of so-called idiopathic dilatation of the oesophagus was not a spasm, but failure of relaxation of the muscle.

Dr. Spriggs preferred the use of the bag to that of the mercurial tube.

Dr. Poynton related a case occurring in a girl after a severe shock.

Sir Charlton Briscoe considered that spasmodic contraction of the crura of the diaphragm might be a factor in causing obstruction in the oesophagus.

Dr. Hurst, in reply, stated that the use of the inflated bag was not unattended with danger. He had seen five cases in which it caused a fatal termination. The mercury tube was much safer. It should be thick and should be left in position for a quarter of an hour before meals. He considered the X-ray appearances excluded the action of the diaphragm as a factor.

5. Dr. J. M. H. Campbell on the *distribution of exophthalmic goitre in Great Britain and Ireland* gave figures based on the deaths during seven years as shown by the



## ASSOCIATION OF PHYSICIANS

Registrar-General's unpublished statistics. Nearly 4,000 deaths were included in this period. Exophthalmic goitre was most common in the west of England, in Cornwall, Devon, and Somerset: in Wales (excluding Glamorgan and Monmouth), in Lancashire, Cumberland, and Westmorland, and in the southern counties of Scotland along the border. Oxfordshire, the North and East Ridings of Yorkshire, and Lincolnshire also had a high incidence. He regarded the figures for Ireland, which showed an extremely low recorded mortality in the western part, as unreliable. The differences in the distribution of the disease were considerable. In the west of England the deaths were more than twenty per million, whilst in the Midlands they were only eleven, and in London, Essex, Hertford, and Middlesex, adjacent counties, the rate was less than eight per million of population living. The evidence suggested that in England (as is the case around the Great Lakes of North America) goitre and exophthalmic goitre occurred frequently in the same localities.

Professor Murray's experience concurred with Dr. Campbell's figures. He referred to the increase of exophthalmic goitre since the war and to its greater frequency in males.

Dr. Langdon Brown pointed out the great frequency of both forms of goitre in the Chiltern Hills and the relative rarity in the adjacent clay district of Essex.

Professor Monro stated that the frequency of goitre in the neighbourhood of Glasgow had been affected to a striking degree by changes in the source of the water-supply.

Professor Muirhead and Dr. Hutchison joined in the discussion.

2-3 p.m.

1. Demonstration of clinical cases (40) in the large hall of the Anatomy Department.

2. Exhibition of pathological specimens collected and arranged by Drs. A. D. Fraser, G. Hadfield, and A. T. Todd. Amongst the many interesting features of this exhibition were the series of fine microphotographs illustrating various diseases such as encephalitis lethargica, the myocardial changes in acute rheumatism, &c.

3. A collection of old Herbals shown by Dr. Neild.

4. Prehistoric remains from the Mendip Caves, shown by the University Spelaeological Society.

## AFTERNOON SESSION

3 p.m.

1. Professor A. J. Hall and Dr. V. G. Townrow (introduced) recorded a case of *primary pneumococcal pericarditis* in a youth of 17. After paracentesis on the third day of the disease, the pericardium was opened and drained on the ninth day. Four weeks later a small empyema at the left base required draining. After this recovery was steady and complete.

2. Dr. R. C. Clarke gave an account of the post-mortem findings in a series of cases of *congenital heart disease in infants*.

Drs. Lapage, W. Collier, and Lewis Smith discussed the communication.

3. Dr. G. A. Sutherland recorded two cases, one a boy of 15 and the other a woman of 37, exhibiting heart-block, which he regarded as cases of that rare condition *congenital heart-block*. In most of the cases previously recorded the chief symptom was dyspnoea on slight exertion. He regarded the prognosis as good.

Dr. Clarke and Professor McIlwaine gave their experience of similar cases.

Professor Wardrop Griffith questioned the congenital origin of Dr. Sutherland's cases.



## OF GREAT BRITAIN AND IRELAND

4. Dr. P. Hamill on *residual dyspnoea in digitalis therapy and the value of atropin* stated that in some cases of cardiac failure, especially valvular disease with fibrillation, under treatment with digitalis the improvement as regards dyspnoea was not comparable with that in the general clinical condition. It seemed probable that digitalis might cause broncho-constriction by central action on the vagus centre in the medulla. Atropin in full doses commonly gave relief to some extent in orthopnoea, and occasionally great relief. It was often of value in aiding the clearing up of residual congestion in such cases. Animal experiments showed that intravenous injections of digitalis or strophanthin caused broncho-constriction, which was relieved by atropin. This did not occur if (1) the medulla were destroyed, (2) the vagi were cut, which showed that the effect was central.

5. Dr. G. A. Allan described the results of investigations on the *load added to the work of the heart by valvular lesions*, which he had obtained by means of a schema of the circulation with a variable distributing valve allowing of different lengths of systole and diastole. By the apparatus different valvular lesions could be imitated. The conclusions he drew from this were that aortic and mitral stenosis both reduced the output 10 to 20 per cent., mitral incompetence 50 to 60 per cent., and aortic incompetence 60 to 70 per cent.

6. Dr. J. Parkinson and Dr. Clark Kennedy (introduced) recorded two cases of *severe heart failure with normal rhythm*, and discussed the causes of this condition. Heart failure with normal rhythm they attributed mainly to chronic lung disease, high blood-pressure, cardio-vascular syphilis, coronary occlusion, and acute infections of the heart: heart failure with auricular fibrillation to chronic myocardial disease.

7. Dr. Batty Shaw exhibited a heart showing a hugely dilated left auricle from an adult—causing pulsation in the right axilla. He also made some remarks on the meaning of the terms pulmonary tuberculosis and consumption.

The Annual Dinner was held at 7 for 7.30 p.m. at the Red Lodge, by permission of the Bristol Savage Club. The President, Dr. Parker, was in the chair. The official guests were Alderman J. Fuller Eberle, the Vice-Chancellor of the University (T. Loveday), Professor Buckmaster, Mr. H. E. Roslyn (Secretary of the Savage Club), Dr. Hadfield, and Dr. A. D. Fraser. 110 members and guests were present.

### SATURDAY, JUNE 7, 10 a.m. MORNING SESSION

1. Dr. E. P. Poulton and Dr. W. W. Payne (introduced) on *observations on diet in relation to insulin treatment*. The ketogenic-antiketogenic ration was calculated for patients with diabetes, and compared with the ketosis was found to run parallel with the blood-sugar, disappearing as the blood-sugar fell, and bore no relation to the  $\frac{K}{A}$  ratio. The physiological action of certain vegetables in raising the blood-sugar in diabetics had been tested. Vegetables were given with a standard breakfast in weights equivalent to 15 gm. of glucose according to Atwater's tables. Carrots, artichokes, and turnips caused about half the rise in blood-sugar of that caused by tomatoes and cabbages.

Dr. Spriggs referred to the unreliability of analyses of vegetables, and stated that boiled turnips had the same food value as green vegetables.

Dr. R. Hutchison agreed with Dr. Spriggs as to the unreliability of analysis of vegetables. The form of carbohydrate varied greatly in different vegetables. Also the absorbability of the carbohydrate value varied greatly in vegetables and in individuals.

Dr. Nesbitt and Dr. Poulton joined in the discussion.

2. Dr. George Graham discussed the *relation of infection to diabetic coma*. Nine cases of coma had been seen, and in all but two some infection was present. (1) Acute otitis media, (2) gangrene of lung and phthisis, (3) pulmonary tuberculosis, (4) influenza, (5) influenza and pus in antrum, (6) parotid abscess, (7) swelling of knee-joint.

## ASSOCIATION OF PHYSICIANS

Comatose patients with an acute infection required much more insulin than patients without infection. He emphasized the importance of looking for the signs of any other disease in all cases of diabetes mellitus.

Dr. Spriggs had noticed considerable local reaction after administration of insulin and variations in strength of different batches of insulin, and asked if this had been noticed by others.

Dr. Poulton suggested that the local reaction might be due to acidity of the insulin. He agreed as to the importance of infection in causing coma. He suggested that the rise of blood-sugar was a protective mechanism, and if so, was it wise to attempt to reduce it?

Dr. Hurst asked if the temperature had been observed in Dr. Graham's cases. It was generally stated that the temperature is subnormal in diabetic coma, but in cases he had observed there was hyperpyrexia.

Dr. Graham, in reply, had found that some patients could take American and not English insulin, and vice versa, without local reaction. Test animals (rabbits) varied greatly in toleration, and therefore standardization is liable to inaccuracy.

3. Dr. A. Dingwall Fordyce discussed *thyroid therapy in cases of glycosuria in children*. Non-diabetic recurrent glycosuria he regarded as primarily (1) nervous, (2) digestive, (3) endocrine, in origin. Cases under (2), when due to excessive fat, sometimes benefited by thyroid extract, but diabetic treatment was preferable. Cases under (3) often benefited by suitable thyroid therapy. Instability of thyroid activity was marked in children and the result of thyroid therapy consequently was varied.

4. Sir J. Purves-Stewart gave a *cinematograph demonstration of cistern puncture*, and discussed the indications and contra-indications of this method in diagnosis and treatment. This was followed by a long and interesting discussion in which several members took part.

5. Dr. W. E. Hume on *some observations on the use of diuretics*. He exhibited a series of charts showing the effects of drugs in cases with oedema. He concluded that members of the caffeine series were useful in cases of heart failure with normal rhythm, but harmful in cases of nephritis.

6. Dr. Carey Coombs, with Dr. J. J. S. Lucas (introduced), discussed *familial liability to sudden death*. In 37 out of 56 cases of sudden death there was associated coronary artery disease. The genealogies of several families showed a marked frequency of sudden death amongst the members thereof.

Dr. Parkes Weber, Dr. Tyson, Dr. Tidy, and Dr. Williamson discussed this communication.

7. Dr. H. Morley Fletcher related a case of *periarteritis nodosa* in a man of 27. The duration of the illness was four months. Aneurysmal swellings appeared on the arms, shoulders, and neck. Death was caused by haemorrhage, resulting from an aneurysm in the left kidney. *Post mortem* many aneurysms, varying in size from that of a pin's head to that of a marble, in the pericardium, liver, kidneys, &c., were found. Blood-cultures and the Wassermann test gave negative results.

2-3 p.m.

Another series of clinical cases was exhibited in the Anatomy Department. This included six cases of chronic *manganese toxicosis*.

## AFTERNOON SESSION

3 p.m.

1. Dr. A. M. W. Ellis discussed the effects of *disturbance of the acid-base equilibrium of the blood to the alkaline side*, and described the mechanism by which the body frees itself of excess acids and alkalis whilst maintaining a relatively constant reaction of the blood. He related four cases illustrating the two modes of origin of alkalaemia: (1) overdosing with sodium bicarbonate, and (2) pyloric and high intestinal obstruc-

## OF GREAT BRITAIN AND IRELAND

tion, and discussed the changes produced in the blood. He expressed the opinion that the acid-base equilibrium to the alkaline side might prove more important in disease than one in the opposite direction. He reported the successful treatment of alkalaemia by the administration of ammonium chloride per rectum.

In reply to Sir J. Purves Stewart's inquiry whether tetany was a frequent symptom of hyperalkalaemia, Dr. Ellis stated that tetany was frequently associated with alkalaemia. Tetany was present in one case of bicarbonate poisoning and one of gastric carcinoma, but not in duodenal ulcer.

Dr. Poulton and Dr. Lewis Smith joined in the discussion.

2. In the absence of Dr. Parsons, who was unable to give his communication on *pulmonary abscess*, Dr. Mackey related a case of *pulmonary abscess* occurring during an attack of lobar pneumonia and followed by recovery.

3. Dr. N. Neild discussed the use and interpretation of *variations of dullness in pleural effusions*.

Sir Charlton Briscoe suggested as an explanation of Grocco's triangular area of dullness that this might be due to defective movement of the diaphragm and limited expansion of the lung.

4. Dr. A. G. Gullan recorded his clinical observations on cases of *epidemic encephalitis*. He gave a classification of various types of the disease and advocated the use of sodium salicylate and potassium iodide.

Dr. Gordon Holmes pointed out the persistence of the infection for a long period after the subsidence of the early symptoms. He related the case of a girl who slept with her sister affected with encephalitis lethargica and who developed the disease 18 days later.

Dr. Morley Fletcher drew attention to the changes in the cerebro-spinal fluid which might persist during and even after convalescence.